EXHIBIT 53

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

NICHOLAS HARRISON, *et al.*, Plaintiffs, v. MARK ESPER, Secretary of Defense, *et al.*, Defendants.	No. 1:18-cv-641 (LMB/IDD)

RICHARD ROE, *et al.*, Plaintiffs, v. MARK ESPER, Secretary of Defense, *et al.*, Defendants.	No. 1:18-cv-1565 (LMB/IDD)

DECLARATION OF DR. SHEILA A. PEEL, MSPH, Ph.D., DAC

I, Dr. Sheila A. Peel, do hereby state and declare as follows:

1. I currently serve as the Director of the Diagnostics and Countermeasures Branch of the Center for Infectious Disease Research, as the Walter Reed Army Institute of Research (WRAIR). In the exercise of my official duties, I have been made aware of this lawsuit by counsel from the Department of Defense's Office of General Counsel.

2. I submit this declaration in support of Defendants' Motion for Summary Judgment. I base this declaration on my personal knowledge, and on my expertise on the subject of clinical testing relating to the detection and monitoring of HIV, including the equipment and procedures used by the

Diagnostics and Countermeasures Branch to conduct HIV viral-load testing and HIV-1 genotype testing for clinical and therapeutic monitoring of U.S. service members.

Background and Expertise

3. I currently serve as the Director of the Diagnostics and Countermeasures Branch in the Center for Infectious Disease Research, at the Walter Reed Army Institute of Research (WRAIR). I joined WRAIR as a Department of Army Civilian Scientist in 1999. From 2010 to 2019, I served as the Chief of the Department of Laboratory Diagnostics and Monitoring and the Director of the HIV Diagnostics and Reference Laboratory (HDRL) in the U.S. Military HIV Research Program at the Walter Reed Army Institute of Research.

4. In my current position, I continue to serve as the College of American Pathologist Laboratory Director of HDRL, which serves as the Department of Defense Tri-Service HIV Reference Laboratory. HDRL is the final authority for generation of laboratory evidence for HIV infection status for all U.S. Army and Navy components, and for the U.S Air Force by request.

5. Under my direction, HDRL's laboratory conducts more than a 400,000 HIV screening and confirmatory tests per year, and also provides technical oversight for over 775,000 tests per year conducted by the U.S. Army HIV Force Testing Services contract laboratory in San Antonio, Texas.

6. Under my direction, HDRL also performs, among other things, clinical monitoring of HIV infection (*i.e.*, HIV viral-load tests); HIV RNA and total-nucleic-acid qualitative and quantitative assays for acute and primary HIV infection, detection of HIV viral reservoir, and for HIV-2; HIV therapeutic monitoring (*i.e.*, HIV protease, reverse transcriptase, and integrase genotyping assays); sexually transmitted infection testing (*e.g.*, Syphilis, Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium), Hepatitis B serology and viral load; Hepatitis C serology and viral-load testing, as well as provides surge test support for SARS-CoV-2 testing for the National Capital Region.

7. In addition, I am responsible for managing various clinical, translational, and applied research programs. For example, I direct research programs developing state-of-the-art diagnostics and clinical and therapeutic monitoring for HIV, sexually transmitted infections, blood-borne pathogens, and emerging pathogens of U.S. Military and U.S. National security interest. I also direct clinical laboratory support for vaccine and therapeutic trials, public-health investigations, and operational research applicable to battlefield operations.

8. The laboratories that I manage generate data that is used to inform, revise, or develop Department of Defense and service-specific policies.

9. I also serve as a Subject Matter Expert/HIV Clinical Laboratory Consultant to the Office of the Armed Forces Medical Examiner, the U.S. Medical Entrance Processing Command, the U.S. Army Medical Command, the U.S. Army Surgeon General, the U.S. Army Blood Program, and the Armed Forces Blood Program Office.

10. In addition to my ongoing duties at the HIV Diagnostics and Reference Laboratory and as Director of the Diagnostics and Countermeasures Branch, I was recently detailed to the Office of the Vice President of the United States, where I now serve as an advisor and a consultant to the White House COVID-19 Task Force. My work for the COVID-19 Task Force is focused on coronavirus (in particular, COVID-19) diagnostics and testing.

11. I serve as a peer reviewer for many scientific journals, and serve on numerous national and international committees and technical panels.

12. I regularly consult with other experts in the field—including at government agencies, commercial partners, and nongovernmental organizations—to develop and advance HIV, sexually transmitted infection, blood-borne-pathogen, and emerging-pathogen detection technologies.

13. I have previously served as an expert witness in court-martial proceedings brought pursuant to the Uniform Code of Military Justice.

14. I hold a Master's of Science in Public Health and a Doctorate of Philosophy in Medical Parasitology, both from the University of North Carolina at Chapel Hill.

15. A true and correct copy of my curriculum vitae is attached to this declaration as Exhibit A.

HIV Testing of Service Members

16. I have reviewed several expert reports and declarations that I understand have been submitted by witnesses for the Plaintiffs in these litigation matters. *See Harrison* ECF No. 26-5 (Hendrix Decl.); *Roe* ECF Nos. 270-20 (Hardy Report), 270-43 (Hendrix Report), 270-47 (Hendrix Rebuttal Report), 270-51 (Hendrix Supplemental Report). Respectfully, for the reasons that follow, I disagree with Dr. Hendrix and Dr. Hardy about the practical obstacles associated with conducting HIV viral-load testing in deployed environments. In my view, for the reasons that follow, HIV testing of deployed service members presents significant medical, scientific, and logistical challenges.

Different Types of HIV Testing

17. I have extensive experience conducting and supervising many different types of HIV testing, including HIV screening and confirmatory tests, HIV viral-load tests, and HIV genotype resistance tests. Each of these tests serves different purposes.

18. **HIV Screening Tests.** HIV screening tests are used to determine whether an individual has been infected with HIV. The Department of Defense uses a very sensitive initial screening test for HIV antibodies and "early" proteins of HIV to determine whether someone is HIV-infected. If the initial screening test returns a "reactive" result, a second, supplemental confirmatory test is conducted, which is even more specific, and identifies particular proteins of the virus that confirms a patient's HIV-infection status.

19. **HIV Viral-Load Tests.** HIV viral-load tests are used to determine the amount or concentration of HIV virus in the blood plasma of an individual who is already known to be

HIV-infected. When someone is HIV-infected, there are many parts of the body where the virus can replicate, including in the blood, the genital track (*e.g.*, semen in men, and vaginal fluid in women), in the brain, and in the spinal fluid. But generally, the body component that correlates most strongly with the burden (or concentration) of HIV virus of an infected individual is the blood plasma. That is why HIV viral-load testing is conducted on blood plasma.

20. Some HIV-infected individuals have millions of copies of the HIV virus in their blood during early infection. Without drug treatment, the virus will replicate and disseminate throughout the body of an HIV-infected individual. The body's immune system can control the virus for some time, but without treatment the infected individual's immune system fails and the infection transitions to HIV Acquired Immunodeficiency Syndrome (AIDS).

21. However, with modern treatments and strict adherence to an antiretroviral therapy (ART) medication regimen, a patient's HIV viral load may eventually be so low as to be "undetected" in an HIV viral-load test. If and when that happens, although the patient is still considered to be HIV-infected, they are also considered to be "virally suppressed" or "well-controlled."

22. The term "viral suppression" means to reduce the function and ability of the viral to replicate or grow; the term "well-controlled" refers to a stable reduction in viral replication that is maintained. The term "well-controlled" preceded the use of the term "viral suppression," although they are often used interchangeably.

23. In other patients, either due to a late diagnosis, poor adherence to medication, or development of a biological resistance to medication that reduces its effectiveness, a viral-load test may indicate current or potential virologic failure (*i.e.*, many thousands of copies of virus in the blood).

24. For that reason, HIV viral-load testing is a critical monitoring tool for HIV-infected individuals. The patient's "baseline" viral load is determined at the time of an initial diagnosis, before any sustained ART treatment. An HIV-infected patient is then tested subsequently and frequently—

generally, for the rest of their life—to measure their viral load, in order to determine whether their prescribed ART regimen is currently effective at keeping their viral load suppressed.

25. Eventually, once an HIV-infected individual is virally suppressed—that is, their viral load has been reduced to a very low level and has remained stable for two years—they need only be tested approximately every six months, per guidelines from the Department of Health and Human Services and recommendations from the Centers for Disease Control and Prevention. Generally, it is accepted that an HIV-infected individual is virally suppressed if they have 200 or fewer copies of the HIV virus detectable in their blood plasma. If the viral load is so low that it is below the limit of detection of the viral load test, the viral load is referred to as "undetectable." The precise concentration of virus that must be present in the blood before detection varies across different testing platforms manufactured by different companies.

26. HIV viral-load testing is also important because it may confirm for a physician that an HIV-infected patient is compliant with their current medication regimen, and that the patient's viral infection remains sensitive to their current ART regimen.

27. **HIV Genotype Resistance Tests.** If someone is prescribed ART to treat their HIV, and reports that they are consistently taking their medication, but their viral-load test nonetheless detects a significant concentration of HIV virus in their blood plasma, at that point, most physicians will order an HIV genotype resistance test. The purpose of an HIV genotype-resistance test is to determine whether a patient has become (or has the potential to become) resistant to their current ART treatment regimen, thus rendering the ART medication ineffective (or less effective). In particular, the test is designed to determine whether the particular strains of HIV virus currently in the patient's blood plasma are resistant (or are developing resistance) to whatever ART treatment regime has been prescribed for the patient.

28. HIV is one of the most mutagenic organisms on the planet. It is constantly mutating and changing and adapting, and an HIV-infected patient has many different (and constantly mutating) strains of HIV in their blood. An HIV-infected individual is not infected with one virus, but rather is infected with swarms of different and constantly mutating variations of the virus. Accordingly, it is possible for HIV to develop resistance, over time, to an ART drug regimen—even in patients who take their ART medication consistently. Resistance to medication is even more common (and occurs more quickly) in patients who take their medication inconsistently, or intermittently.

29. HIV genotype-resistance testing permits sequencing of the particular strains of virus in a patient's blood and, in particular, a sequence of the regions of the virus that target the various mechanisms of action of the types of ART drugs used for treatment. After years of clinical studies, it is now known which genetic sequence changes (*i.e.*, mutations) determine resistance to ART drugs, and even which particular genetic sequences signal resistance to a particular drug.

30. Accordingly, HIV genotype-resistance testing can allow a physician to decide whether a particular patient's HIV infection is still sensitive (or is likely to remain sensitive) to the ART regimen that has been prescribed. That information is critically important in informing decisions by a treating physician as to whether to modify the current ART medication regimen in any way. (There are many different types and combinations of medications that all qualify as "ART," and different combinations and regimens are more effective against different strains of the virus than others.)

31. HIV genotype-resistance testing can also strongly indicate that a patient is non-compliant with their medication. Many patients report compliance with their medication who, in fact, are not compliant (or are not always compliant), which creates a risk of a virologic failure and subsequent increase in viral load. If there is a spike (increase) in detected viral load, and subsequent resistance testing confirms that the patient does not have any resistant strains of the virus in their blood, the most likely explanation is that the patient was non-compliant with their medication regimen.

32. Thus, resistance genotype testing is conducted for a number of reasons, including (1) to guide initial selection of the drug regimen for newly HIV-diagnosed individuals entering into medical care, and (2) to guide selection of an active drug against HIV following loss of virologic control (which could be due either to the emergence of drug resistance, or a suboptimal reduction in viral load on the current regimen).

General Processes for HIV Testing

33. Although the purpose of each of these different types of HIV tests is different, the basic process by which each of these tests are conducted is similar.

34. First, a blood sample must be drawn by a trained phlebotomist, from the individual to be tested—that is, in this case, from the service member, wherever he or she may be physically located. The phlebotomist uses a needle to draw blood from the patient's veins, typically from the forearm. The volume of blood required varies by test.

35. The HDRL does not provide phlebotomy services. Instead, blood specimens are acquired at distant sites, and are then transported to HRDL's laboratory in Maryland, as quickly as possible, in accordance with detailed specimen-submission guidelines and chain-of-custody procedures. If those requirements are not adhered to with rigor, the sample may be rejected, or further interactions may be required with those at the testing location to determine whether the sample is of sufficient quality to produce a reliable test result.

36. A true and correct copy of HDRL's current specimen-submission guidelines is attached to this declaration as Exhibit B.

37. If the service member to be tested is physically located within the national capital region (*i.e.*, Maryland, Northern Virginia, or the District of Columbia), then the blood specimen can be sent to the HDRL within a matter of hours, where it can be processed for testing the same day.

38. In most cases, however, a blood specimen is drawn at a distant location, processed (*i.e.*, spun in a centrifuge and separated into its component parts), then immediately frozen, and shipped—across the country, or around the world, if necessary—to our laboratory in Maryland.

39. HIV testing is a very precise, scientific process. For example, to obtain an accurate result from an HIV viral-load test, the plasma component of the blood must be separated from the rest of the blood in a very precise manner. To accomplish that separation, first, the blood is drawn into an "EDTA tube," which is a small cylindrical blood collection tube containing a substance called ethylenediaminetetraacetic acid (EDTA). EDTA is an anticoagulant that has been scientifically verified to prevent blood clotting without affecting HIV test results.

40. The actual separation of the plasma components is accomplished using a powerful centrifuge, which spins the tube of blood at a high rate of speed, creating centrifugal force on the contents of the tube (*i.e.*, the blood specimen) that is approximately 1,600 times stronger than the force of gravity. Depending on the precise test being ordered (and the manufacturer of the centrifuge), the tube is spun by the centrifuge within vary narrow parameters, at a very specific angular speed, for a very specific amount of time.

41. The centrifuges used by the military are instruments routinely used within clinical laboratories. These instruments employ stringent infection control (*e.g.*, transparent locking caps for swing buckets with interchangeable inserts for the various blood collection tube sizes), require semi-annual maintenance to ensure calibration (*e.g.*, accuracy of spin), and access to sufficient electricity.

42. By spinning the blood specimen in a centrifuge at a high speed, we are able to "pellet" or separate the red-blood-cell component of the blood sample from the white-blood-cell component, because of the varying densities of the different components within the blood sample. The white-cell component is also known as the "buffy coat" of the blood sample. The remaining component—the

blood plasma, which is a yellow color after the red cells and the white cells have been removed—is then carefully removed from the EDTA tube, ensuring that there is no inadvertent mixing with the red cells or the buffy coat that are left behind in the EDTA tube.

43. Next, the plasma is carefully divided into aliquots (portions) of the precisely desired volume, in order to carry out whatever test (or tests) the technologist is planning to run, and in accordance with the precise specifications of the particular testing platform. Different manufacturers of HIV testing equipment (*e.g.*, Roche, Abbott Laboratories, *etc.*) call for different testing volumes. The plasma is aliquoted into cryotubes, then frozen for shipment to our laboratory.

44. To maintain what we refer to as the "cold chain" during shipment, a blood sample drawn for HIV testing is frozen at -80 degrees Celsius (-112 degrees Fahrenheit), then shipped in a large container of "dry ice," which is the colloquial term for solid-state Carbon Dioxide (CO_2). Dry ice sublimates at -78.5 degrees Celsius (-109.3 degrees Fahrenheit), so it is able to keep the plasma sample solidly frozen at a very low, stable temperature, as long as it is used in sufficient quantities and is stored in a properly insulated container.

45. We recommend that those who submit samples to the HDRL use at least two pounds of dry ice per every day that the sample needs to remain frozen. So over a 72-hour trip, at least six pounds of dry ice would be necessary. To be safe, we would request about 10 pounds of dry ice for a 72-hour shipping journey.

46. If dry ice is not available, "wet ice" (*i.e.*, normal frozen water of the sort that may be found in a residential freezer) may also be used, at least under certain conditions. But, as the ice melts (at zero degrees Celsius or 32 degrees Fahrenheit), it may not sustain a sufficiently cold temperature for the sample through the duration of the shipping process, depending on how well-insulated the container is and the duration of the trip. For that reason, using "wet ice" to ship a plasma sample

(even over short distances) is considerably inferior to using dry ice. Wet ice should only be used as a last resort, when dry ice is unavailable.

47. If the sample does not maintain a proper temperature during transit, there is a substantial risk of a false-negative test result, which would incorrectly suggest that the patient's viral load is low or undetectable, when in fact it may be high. That outcome is dangerous to the patient (who needs prompt medical intervention to suppress their viral load), and also to others, as an individual who believes he or is she is virally suppressed but in fact is not, has a heightened risk of transmitting the virus to others.

48. Scientific rigor and precision in this process are necessary to achieve the goal of the test: an accurate, estimated count of the number of copies of the HIV virus per unit of volume in the patient's blood plasma. Any inadvertent mixing of the blood plasma with the white cells in the buffy coat may artificially elevate the reported viral load, and thus compromise the test.

49. Once the frozen sample is received in our laboratory, it is accessioned into our Laboratory Information Management system, and then transferred to the Molecular Section where samples are stored, and remain frozen until tested (either the same day or the next day). The frozen plasma samples are removed from the freezer, and thawed at room temperature until just thawed (which takes approximately 20-30 minutes). The plasma is mixed well by inverting the tube several times, then an aliquot is removed and added to a special tube used by the Roche COBAS®AmpliPrep/COBAS®TaqMan® HIV-1 Test, v2.O. The sample tube is placed into the COBAS®AmpliPrep instrument, which processes the sample by extracting the genetic material of the virus, if present, and prepares the sample for nucleic-acid amplification and detection of HIV-1 by the COBAS®TaqMan® 48 analyzer. The test quantifies the amount of HIV-1 RNA (genetic material) of the virus in the sample; it can quantitate over a range of 20 copies to 10,000,000 copies per milliliter of sample.

50. The HIV viral-load testing instruments used by our lab are Roche COBAS®AmpliPrep and COBAS®TaqMan® 48 systems. This system can test 192 samples per eight hours. The COBAS®AmpliPrep is approximately 6 feet in length by 3 feet in width. The instrument runs continuously. Its lines must be flushed with buffer daily, and the unit must be recalibrated if the power fails. The unit is served by a Roche service engineer twice yearly, or within 24 hours if performance does not meet the manufacturer's criteria. The instrument must be housed within an ambient-temperature-controlled space which is maintained within 18 to 25 degrees Celsius (or 66.4 to 77.0 degrees Fahrenheit).

51. All United States FDA-approved HIV viral-load tests are high complexity tests run on automated test systems that require stable power infrastructure and may require dedicated water systems. These testing systems can be massive, and some (for example, the Roche 8800 system) may even require reinforced structural elements, like fortified floors.

52. The test schema requires zonal work flows (separate spaces) to prevent cross contamination by HIV genetic material. This means there must be sufficient space for a Zone 1 "Clean Room," where test reagents are prepared; a separate area with Biological Safety Cabinets for thawing and aliquoting samples (a Zone 2 "Dirty Room"); and, a third area, Zone 3, for the actual amplification and detection of HIV-1 viral load. It is critically important to manage samples and all test work flows to avoid contamination, as one copy of HIV genetic material can be amplified to over 1 million copies.

53. A series of internal-control tests are also simultaneously run on the blood sample—not for the purpose of measuring the concentration of virus in the blood, but to confirm whether or not the sample itself was valid and suitable for testing (*e.g.*, whether the proper anticoagulant was used to collect the blood specimen, whether some inhibitor is present in the sample that might distort the

results, *etc.*). If a sample fails any of the internal-control tests, the patient's results are set aside, and the remainder of the test run is pushed forward to a second technologist.

54. After the full testing process is completed and a tentative result is obtained, the result is presented by the technologist to his or her supervisor, who will ultimately release the results back to the entity that submitted the sample.

55. Before any results are actually released, however, a third lab employee will perform a clinical data check, to ensure that all of the metadata associated with the blood sample and test results have been accurately recorded, and that the results are to be released to the correct physician and patient. This requires confirming, for example, the patient's first name, last name, date of birth, private health information, personal identifying information, and similar data.

56. After all of these controls are satisfied, the test result is released back to the entity that submitted the sample, for purpose of informing treatment decisions to be made by the patient's treating physicians.

57. A rigorous chain of custody is maintained throughout this entire process.

Obstacles to HIV Testing of Deployed Service members

58. Virtually none of the equipment and capabilities described above are readily available to forward-deployed service members. Such locations often are accompanied by only the most basic of medical assets. Accordingly, carrying out the full process of laboratory-quality HIV testing in forward-deployed conditions is not practically possible. Instead, the only possible alternative, as a practical matter, is (1) that the deployed service member be transported to a Role 2 Medical Facility where a blood specimen can be drawn, immediately processed via centrifuge, and then frozen; (2) the sample is stored in dry ice and shipped to the HDRL in Maryland, and (3) the actual testing is carried out in Maryland.

59. Department of Defense medical facilities are categorized into three tiers. A Role 1 Medical Facility may vary, but typically may provide primary healthcare, specialized first-aid, triage, resuscitation, and stabilization. Basic Role 1 capabilities are routine sick call and the management of minor sick and injured personnel who can immediately return to duty. Role 1 also includes preparation of casualties for evacuation to the rear. A Role 1 medical facility cannot provide phlebotomy services or centrifuge a blood sample.

60. Role 2 can be divided into Role 2 Light Maneuver (LM), which are mobile medical units designed to support land maneuver formations. A Role 2LM medical unit is able to conduct advanced resuscitation procedures up to damage-control surgery, but has no ward beds. A Role 2 Enhanced facility provides basic secondary healthcare, built around primary surgery, an intensive-care unit, and ward beds. A Role 2E medical facility should be able to stabilize post-surgical cases for evacuation. A Role 2 medical facility will typically be able to provide phlebotomy services, and may (or may not) have a centrifuge and sufficient supplies of dry ice. The nearest Role 2 medical facility to a deployed service member may or may not be easily accessible, depending on the location and the circumstances of deployment.

61. A Role 3 medical facility is staffed and equipped to provide care to all categories of patients, to include resuscitation, initial wound surgery, specialty surgery (general, orthopedic, urogenital, thoracic, ENT, neurosurgical) and post-operative treatment. Role 3 medical facilities are akin to basic civilian hospitals, and are typically located far from the theater of war.

62. The Role 2 medical facility, to draw and process an adequate blood sample and prepare it for shipment, must have at least the following minimum capabilities available:

a. Phlebotomy supplies, for drawing blood (*e.g.*, at a minimum, gloves, alcohol or iodine to cleanse the area, a tourniquet, tubes, a tube holder, needles, tape, and gauze, correct blood collection tubes).

b. A trained phlebotomist to perform the blood draw.

c. Clinical centrifugation capability to separate blood components (*e.g.*, a centrifuge, to isolate the blood plasma).

d. A cryovial that can withstand freezing.

e. The ability to aliquot samples (*e.g.*, pipets, sterile tips).

f. Strict cold-chain management (*e.g.*, the capacity to freeze and store plasma samples at -80 degrees Celsius, until the sample can be transported to a high-complexity test laboratory like HDRL).

g. Sufficient quantities of dry ice to keep the sample fully frozen through the duration of shipment from a distant location around the world to the HDRL in Maryland.

h. Ability to ship to a high-complexity U.S. military test laboratory like HDRL. This may require rearrangement with receiving and perhaps transit laboratories to ensure continued cold-chain management. This also may require freezing for a longer period of time until a military transport option is available, due to the lack of private (*e.g.*, FedEx, UPS, or DHL) freight capability in the relevant Area of Operations. This may also require a route through a higher-level facility (*i.e.*, Landstuhl Regional Medical Center in Landstuhl, Germany for samples taken from CENTCOM) before arrival at the final laboratory destination (*i.e.*, HDRL in Maryland).

63. My understanding is that Plaintiffs in these litigation matters have attempted to paraphrase some of my deposition testimony in this case as follows: "it would likely not be a problem to collect a blood specimen at a Role 2 medical facility and transport it on a helicopter to a Role 3 medical facility for processing." Pls.' Mot. for Summ. J., Statement of Undisputed Facts, *Roe* ECF No. 270, ¶ 73. Respectfully, that is not an accurate paraphrase of my deposition testimony.

64. In particular, that statement ignores the fact that transportation within (or in and out of) a deployed environment is often quite logistically challenging, financially costly, and, most importantly, may endanger the safety of the service member-patient and all those who must travel with him or her (including, for example, pilots and drivers). I know from my own personal experience in working to obtain blood samples from deployed service members that it is no small endeavor to transport a deployed service member to a Role 2 medical facility, and every such trip presents non-trivial risks to the service member to be tested and many others (in addition to significant financial costs on the Department of Defense).

65. I am also aware from my own personal knowledge and experience that service members are often deployed to locations, for extended periods of time, from which neither Role 2 nor Role 3 medical facilities are easily accessible.

66. In addition, I know from my own personal experience in working to obtain blood samples from deployed service members that commercial shipping options within (or in and out of) a deployed environment are often impractical or non-existent. For example, many private shipping companies (*e.g.*, FedEx, UPS, DHL, etc.) do not operate in any significant capacity—or at all—in or around the locations of deployed service members (particularly in significant portions of the CENTCOM region).

67. Those logistical problems have only gotten more severe recently, as the new Department of Defense construct for warfare has increasingly moved to a Multi-Domain Operations (MDO) model. The MDO construct is premised on the assumption that small expeditionary forces will be pushed far forward into near peer-to-peer battle space; warfare will no longer be fought with large ground forces advancing with readily available medical assets and logistical supply lines. *See* Ex. 3, TRADOC Pamphlet 525-3-1, *the U.S. Army in Multi Domain Operations*. This has many significant

consequences from the perspective of those (like me and my colleagues at HDRL) who are responsible for diagnostics in support of medical treatment of deployed service members.

68. For example, we can no longer assume the consistent availability of so-called "golden hour" MILAIR medical evacuations—that is, risky extraction of severely injured or ill personnel by helicopter within an hour (*i.e.*, "the golden hour") may not be possible. Rather, patients may have to be stabilized for a day, several days, or even several weeks in near-peer battle scenarios. This increases the risk to an HIV-infected service member and their peers. For example, if they lose or run out of medication, this could result in viral rebound and an increase in viral load (which also increases the risk of transmission to others). And if there is a significant health issue associated with their infection, medical help will not be as quickly or as readily available as used to be the case. Service members are now routinely retained in forward Areas of Operations (AORs) with minimal to no medical assets for lengthy periods of time.

69. Under this model, when trying to medically manage service members (including HIV-infected service members), the only options are to bring doctors and laboratories to the service member-patients, or to bring the service member-patients to doctors and laboratories. That is a serious challenge in an area of open conflict, where you can never be sure that you will have access to the necessary medical personnel, equipment, or supplies.

70. As a result, the Department of Defense's current focus is on force readiness of medically ready, world-wide-deployable service members. Deployment of service members who may require frequent (and sometimes unpredictably timed) transport out of far-forward-deployed locations to Role 2 or Role 3 medical facilities substantially complicate that goal.

Using One Centralized HIV Testing System for Service Members Has Significant Benefits

71. My understanding is that Plaintiffs in these litigation matters have also stated that "[a] blood specimen does not necessarily need to be shipped to the HIV Diagnostics and Reference

Laboratory (HDRL) in Silver Spring, Maryland, for a viral load test to be conducted, as is the current practice." Pls.' Mot. for Summ. J., Statement of Undisputed Facts, *Roe* ECF No. 270, ¶ 74.

72. That may be a literally true statement because, technically, samples could be drawn and processed via centrifuge at a Role 2 medical facility, and then frozen and shipped to another Role 3 medical facility (or its equivalent) other than the HDRL in Maryland—for example, there are many sophisticated public and private laboratories in Europe. But the current system, in which the vast majority of HIV testing of U.S. service members is conducted in one centralized system (and with respect to the Army and the Navy, at one laboratory), has significant advantages for patient care over the system hypothesized by Plaintiffs, in which the military would contract with various public or private laboratories around the world. Specifically, for the reasons that follow, it would often be difficult or impossible to make meaningful comparisons of current viral load data to historical, baseline viral load data for each patient, which could lead to less-informed physicians and, potentially, worse patient outcomes. And at a minimum, testing costs, testing frequency, and the associated burdens on service members—and the unavoidable risks associated with service member travel for testing—would increase.

73. Whenever possible, physicians prefer to order HIV testing from the same testing laboratory repeatedly, because they can expect consistency in results that better informs their treatment decisions.

74. Every FDA-approved HIV testing system has different sensitivity thresholds (*i.e.*, the minimum amount of virus that must be present in the blood plasma before a reactive result is triggered and can be measured). So, for example, if a laboratory needs to replace an outdated piece of testing equipment, it will typically try to replace the equipment with another testing machine from the same manufacturer, in order to avoid having to switch to an entirely new system with a different sensitivity threshold. In the event of replacing an existing instrument with a newer or updated version from the

same manufacturer, a letter of equivalency is issued by the manufacturer attesting that the test performed on the new instrument is equivalent to that run on the replaced instrument.

75. If a patient receives one set of tests results from one system, and another set of test results from another system (*e.g.*, the first set of tests was run on a machine manufactured by Roche, but the second set of tests was run on a machine manufactured by Abbott Laboratories), it may be difficult or even impossible to meaningfully compare and analyze small changes (or perceived changes) in a patient's HIV viral load.

76. For that reason, it is standard practice to conduct additional tests to "rebaseline" patients if a patient (for whatever reason) is being tested at a different laboratory with different equipment than that used for previous tests. Similarly, even within the same laboratory, if a laboratory has changed to a new piece of testing equipment with a different sensitivity threshold, a laboratory will typically send a letter out to each patient or physician, informing them that the laboratory recently changed its testing platform, and is therefore asking for a new, additional blood sample to conduct new baseline viral-load tests. That way, if there are future increases (or perceived increases) in the patient's viral load, they can be measured against an accurate baseline, calculated from the same equipment with the same sensitivity threshold.

77. Although it is inconvenient and costly for the patient (and for the Department of Defense, in the case of U.S. military service members), this "rebaselining" process is important to maintaining the proper standard of care for an HIV-infected patient. Without this "rebaselining" process, it would be difficult to determine whether an increase in a patient's viral load measurement actually represents potential virologic failure—for example, because the patient has recently become non-compliant (or inconsistent) with his or her adherence to medication, or because the patient is developing a resistance to their current medication regimen through no fault of their own—or, on the other hand, whether the perceived increase represents a harmless one-time anomaly in the patient's

testing results that can be safely ignored by the treating physician, assuming the next test returns a lower viral-load result. Such one-time anomalies are not uncommon.

78. Accordingly, in part to minimize the need for rebaselining, additional testing costs, and additional testing burdens on patients, and to provide the best possible information to service members and their treating physicians, both the Army and the Navy do the vast majority of their HIV viral-load testing at the HDRL laboratory in Maryland. The Army and the Navy generally do not contract with private laboratories—either in the United States, or abroad—to do HIV viral-load testing of service members. This is a conscious, and science-based policy choice, which is superior to spreading testing over a variety of public and private labs around the world, for the reasons described above.

79. Similarly, the Air Force does the vast majority of its HIV viral-load testing at a laboratory at the San Antonio Military Medical Center (SAMMC), in Fort Sam Houston, in San Antonio, Texas, with certain testing (in complex cases) done, by request, at another similarly situated military laboratory (*i.e.*, the HDRL laboratory in Maryland, which I supervise). The HIV testing laboratory at SAMMC uses the same equipment as the HDRL lab in Maryland, so rebaselining is not necessary, should a service member receive testing data from both locations.

80. Different public and private laboratories around the world use a wide variety of testing platforms, with varying sensitivity thresholds. Were the Department of Defense to contract with a wide variety of public and private laboratories around the world to conduct HIV testing, frequent rebaselining would be necessary in order to provide useful testing data to service members and their treating physicians. That would impose additional risks for service members (both the patient to be tested, and any others who are assisting in their transport to and from their deployed duty location, including in and out of deployed environments, if necessary) and additional costs on the Department

of Defense (which would have to pay for all of the additional tests that would be unnecessary if all testing was conducted within the same system).

There are no FDA-Approved Point-of-Care Tests for HIV Viral-Load Testing

81. As described above, the process of conducting accurate and reliable HIV testing—of anyone, let alone of a military service member in a deployed environment—is complex and logistically challenging.

82. As a result, there are currently no "point-of-care" (or "point-of-donation," for screening potential blood donors) HIV viral load or HIV-1 resistance genotyping tests that are approved by the United States Food & Drug Administration (FDA)—for either the civilian population, or for military service members.

83. HIV is classified as a Class-III pathogen. Accordingly, all tests must be FDA-approved through Pre-Market Application Clinical Trials regulated by the FDA Center of Biologics Evaluation and Research. Accordingly, both federal law and Department of Defense policy prohibit the use of non-FDA-approved HIV tests.

84. There are point-of-care serological HIV antibody tests which have been used during urgent, emergent mass-combat-casualty care scenarios when all licensed blood products have been exhausted and urgent blood donations are necessary to save the life of a service member. In these situations, the "walking blood bank"—that is, nearby service members—line up and donate blood in real time. In these circumstances, there is generally no time to perform screening of blood donation units as mandated by the FDA; instead, only minimal tests for cross match and typing of blood units is conducted. If there is time during these scenarios, point-of-care (rapid device tests) for detection of HIV antibodies, may be used to screen potential blood *donors*, although not the actual blood units (*i.e.*, the donated blood itself). If a service member's blood yields a reactive test result on one of these tests, they should not be allowed to donate blood.

85. These tests have known false-negative and false-positive rates; and they are not FDA-approved for screening of blood donations, rather they are only FDA-approved as an aid in diagnosis of HIV infection. Nevertheless, the United States military has used these tests in urgent mass-casualty scenarios to mitigate the risk of the administration of "hot blood" (that is, unlicensed blood product). Because of their comparatively high error rates, a reactive result on one of these tests is only considered a "presumptive positive," and must still be confirmed by additional supplemental confirmatory tests.

* * *

In accordance with 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed this 01 June, 2020.

PEEL.SHEILA.A.1239535719

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Laboratory Director, HDRL; LDL
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EXHIBIT A

Curriculum Vitae

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Federal Rank: GS 15 Supervisory Health Science Administrator

Education

Ph.D.	University of North Carolina at Chapel Hill, Doctor of Philosophy, Major: Molecular Parasitology, Minor: Pharmacology, December 1991.
M.S.P.H.	University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill, NC, Master of Science in Public Health. Emphasis Medical Parasitology, December 1986
B.A.	University of North Carolina at Chapel Hill, Chapel Hill, NC, Bachelor of Arts in Zoology, May 1981.

Professional Experience

2020 to date: Office of Vice President, United States, Advisor/Consultant in support of the White House COVID-19 Task Force – Diagnostics

2020 to date: Director, Diagnostics and Countermeasures Branch, Center for Infectious Disease Research, Walter Reed Army Institute of Research**.**

2014 to date: Laboratory Director, College of American Pathologist, Leishmania Diagnostic Laboratory, Walter Reed Army Institute of Research.

2010 to 2019: Chief, Department of Laboratory Diagnostics and Monitoring, U.S. Military HIV Research Program, Walter Reed Army Institute Research

2005 to date: College of American Pathologist (CAP) Laboratory Director, HIV Diagnostic and Reference Laboratory, Department of Laboratory Diagnostics and

Monitoring, U.S. Military HIV Research Program, Walter Reed Army Institute Research

2009-2010 **Acting Chief, Department of Laboratory Diagnostics and Monitoring, Division of Retrovirology,** Division of Retrovirology, Walter Reed Army Institute Research

2006-2010 **Assistant Chief, Department of Laboratory Diagnostics and Monitoring, Division of Retrovirology,** Division of Retrovirology, Walter Reed Army Institute Research

2003-2005 **Assistant Chief, Department of Molecular Diagnostics and Pathogenesis,** Division of Retrovirology, Walter Reed Army Institute Research

2001-2004 **Chief, Flow Cytometry Resource Laboratory,** Department of Molecular Diagnostics and Pathogenesis, Division of Retrovirology, Walter Reed Army Institute Research

2000-2005 **Chief, De Novo Print Microarray Laboratory,** Department of Molecular Diagnostics and Pathogenesis, Division of Retrovirology, Walter Reed Army Institute Research.

1992-1993 **Research Instructor**, University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill, NC, Department of Epidemiology.

1974-1985 **Medical Technologist**, University of North Carolina Hospitals, Clinical Microbiology and Immunology Laboratories, Chapel Hill, NC, Medical Technologist Clinical Diagnostic Bacteriology.

Consulting and Postdoctoral Experience

2012 to 2016 **U.S. Military Courts Martial Expert Witness/Consultant – Army, Navy, Air Force Prosecution Teams**, Diagnostics/Clinical Monitoring HIV and related diseases

2003 to date **Subject Matter Expert**, Diagnostics/Clinical Monitoring HIV and related co-morbidities

2001 to date **Subject Matter Expert,** Quality Management/Assurance, Clinical Laboratory Medicine

2000-2005 **Subject Matter Expert,** Functional Genomics and Bioinformatics: US Army Medical Research Material Command

1997 **Technical Advisor**, Tropical Disease Research Drug Discovery Program, World Health Organization, Geneva, Switzerland. Advisor on technical panel for drug intervention strategies for global emerging and re-emerging parasitic diseases.

1996-1999 **Distinguished National Academy of Sciences, National Research Council, Resident Research Associate**. Department of Parasitology, Drug Development

and Discovery Section. Walter Reed Army Institute of Research, Division of Experimental Therapeutics

1993-1996 **Postdoctoral Fellow**, University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill, NC, Dr. Ralph S. Baric, Department of Epidemiology.

Honors

2019 **Order of Military Medial Merit:** private organization founded by the Commanding General US Army Health Services in 1982. Recognition for highest standards of integrity, moral character, professional competence, selflessness, and sustained contributions to the betterment of Army Medicine.

2014 **Superior Civilian Service Award:** Major General Joseph Caravalho, 21 July 2014. Commended for outstanding service as Supervisory Health Science Administrator in support of highly collaborative interagency working environment and development of countermeasures for HIV and diseases of military relevance.

2010 **Commander's Award for Civilian Service:** COL Kent E. Kester, March 4, 2010. Commended for exceptional service as Laboratory Director, Department of Laboratory Diagnostics and Monitoring in support of RV144, the world's first successful HIV vaccine trial.

2008 **Commander's Coin:** COL Thomas Logan, Acting Commander, Center for Health Promotion and Preventative Medicine. 2008. Meritorious service as HIV EPICON Task Team Member.

2005 **Department of Army SBIR 2005 Quality Award:** Claude M Bolton, Jr., Assistant Secretary of Army for Acquisition, Logistics, and Technology. Meritorious service for technical oversight of SBIR Phase II contract "Development of Web-enabled Platform for Microarrays". Directed commercial partnership for development of Laboratory Information Management System (LIMS), and Analytical Information Management System (AIMS).

2002 **U.S. Army Research and Development Achievement Award**. Meritorious service in leading the establishment of state-of-art functional genomic technologies to accelerate US Military biomedical research efforts.

1996-1999 **National Academy of Sciences, National Research Council, Resident Research Associate**, Walter Reed Army Institute of Research, Washington, DC

1991 **Delta Omega**, Public Health Honor Society

Membership on Technical Panels, Technical Panels/Boards

2018-2019 Member, Revision Panel, Army Regulation (AR) 600-110, *Identification, Surveillance, and Administration of Personnel Infected with Human Immunodeficiency Virus.* Designated SME for revision of all sections pertaining to laboratory screening/diagnosis.

2018	Temporary Member, US FDA Blood Product Advisory Committee: advisory panel for consideration of reclassification of HIV from class III to class II pathogen
2016-2018	DOD Representative, USG Global Diagnostics Working Group
2016-2018	DOD Representative, Viral Load Task Force, PEPFAR
2014-2017	DOD Representative, Laboratory Technical Working Group, PEPFAR.
2013-2017	Technical Co-chair, Integrated Product Team, Whole Blood Transfusion Transmitted Disease Rapid Diagnostic Device, US Army Medical Research and Materiel Command.
2013	Member, organizing Committee, Vaccine-Induced Sero-Positivity (VISP), 14-15 March 2013. Global HIV Vaccine Enterprise sponsored invitational meeting to formulate best practices for management of durable VISP/R within vaccine trial participants; summarize progress toward commercially-available differential tests; review current vaccine candidate pipeline and impact on differential HIV test(s); and, explore opportunities for collaborations in addressing VISP.
2012-2017	Technical Consultant, Center for Disease Control HIV Incidence and Case Surveillance Branch. Member, Technical Consultancy for revision of current public health case definition for HIV infection among adults and children and clinical staging of disease in the U.S.
2011-2016	Member, US Interagency Diagnostics Working Group to identify and bridge execution of diagnostics across Agencies for efficiencies/effectiveness
2010-2011	Member, Revision Panel, Army Regulation (AR) 600-110, *Identification, Surveillance, and Administration of Personnel Infected with Human Immunodeficiency Virus.* Designated SME for revision of all sections pertaining to laboratory screening/diagnosis. First complete revision of AR 600-110 since 1986.
2009:	Chair, Source Selection Board, $50 M Centers for Health Care Contracting, Health Services Contract, USA Medical Command, San Antonio, TX (August 2009)
2008-2009:	Co-Chair, Viral Panel Working Group: USG, NGO, Academic working group for development of updated, dynamic HIV-1 panel to support cross-platform comparisons, development of HIV molecular/serological screening, diagnostic, and/or monitoring technologies. Sponsored by Division of AIDS, NIAID, NIH.
2006-2017:	Member, Association of Public Health Laboratory/CDC HIV-Laboratory Algorithms Working Group. Develop recommendation for next generation algorithms for HIV screening, diagnosis for US population.
2006-2018:	Member, trans-Agency Global AIDS Program Technical Laboratory Working Group. Develop national strategic plans for tired laboratory services; standardize training for laboratory services, implementation Quality Systems Management

standards for President's Emergency Plan for AIDS Relief (PEPFAR) target countries.

2007-2009: Global AIDS Program Laboratory Study Section, Reviewer PEPFAR Country Operational Plans

2006-2009: Member, Global AIDS Program Molecular Diagnostics Subcommittee. Develop comprehensive guidelines for infant diagnosis of HIV, HIV-1viral load measurements, and drug resistance surveillance for PEPFAR target countries.

2006-2008: Defense HIV AIDS Program Member, Global AIDS Program HIV Diagnostics Subcommittee. Development of comprehensive guidelines/standards for HIV detection/diagnosis for PEPFAR target countries

2006-2018: Member, U.S. Department of Defense/Nigerian Ministry of Defense Emergency Plan Implementation Laboratory Technical Working Group.

2006: Member, Source Selection Board, $80M Centers for Health Care Contracting, Health Services Contract, USA Medical Command, San Antonio, TX (September 2006)

2004-2005: Chair, DoD Bioinformatic Working Group on Information Management. Tri-Service (Army, Navy, Air Force) initiative to define current state-of-practice, identify gaps and impediments in current capabilities, and chart roadmap for DOD research community

Committees

2013 to date: Acting Chair (rotating assignment), WRAIR Institutional Review Board.

2010 to date: Senior Member, WRAIR Institutional Review Board. Appointed, January 2010

2009: Chair, Stand up of Laboratory IT Requirements Working Group, Walter Reed Army Institute of Research, Appointed, August 2009. Develop recommendations and roadmap to ensure IT infrastructure will support execution of cutting edge and rapidly evolving state-of-art clinical and research efforts.

2009: Observer, Clinical Laboratory Standards Institute Subcommittee on Criteria for laboratory Testing and Diagnosis of HIV-1 Infections. Development of new clinical diagnostic guidelines for HIV screening, diagnosis.

2009: Member, Program Committee, Association of Public Health Laboratory/CDC, 2010 HIV Diagnostics Conference.

2008 to date: Member, HIV Vaccine Trial Network, HVTN 505 Clinical Trial Laboratory Operations Group.

2007-2008: Member, PAVE100 Laboratory Operations Group. Development of HIV-1/HIV-2 screening and diagnostic algorithms and Manual of Operations for multinational DNA-prime boost HIV-1 vaccine trial.

2005-2006: Member, Steering Committee, Form CD4 Working Group

Briefings (sample):

2020 Secretary Defense, COVID-19 Response – Diagnostics, 17 March 2020

2020 Secretary Army, COVID-19 Task Force – Diagnostics - ongoing weekly

2019 Brigadier General Michael Talley, Medical Research and Development Command, "Cource of Action Brief, Bldg 568, Ft. Detrick, MD (December 2019).

2019 Major General Barbara Holcombe, Medical Research and Materiel Command, "Cource of Action Brief, Bldg 568, Ft. Detrick, MD (July 2019).

2018 Major General Barbara Holcomb, Medical Research and Materiel Command. "US Army HIV Force Testing Business Case Analysis" (Mar 2018).

2016 Major General Brian Lein, Medical Research and Materiel Command. "US Army HIV Force Testing" (Dec 2016; Jan 2017; Feb 2017).

2014 Major General, Joseph Caravalho, Jr. Medical Research and Materiel Command. "US Army HIV Force Testing" (Mar 2014).

2010 COL Loren Erickson, MD, DrPH, FACPM, MS, Command Surgeon, HQ USCENTCOM/CCSG, "US ARMY HIV Diagnostic Algorithm and Implications for Deployed Personnel". (Jan 2010)

2009 Major General Gilman, Commanding General, US Army Medical Research and Materiel Command. (AUG 2009) "Missions of HIV Diagnostic and Reference Laboratory in support of the War Fighter".

2009 Mr. Keith Webster (AUG 2009), The Deputy Assistant Secretary of the Army for Defense Exports and Cooperation. "US Military HIV Research Program International Activities".

2009 Mr. Herbert Colley, Chief of Staff, Office of the Surgeon General (Feb 20), Use of Rapid Tests for Battlefield Pre-donation Detection of Transfusion Transmission Disease

2008 Mr. Thresher, Chief of Staff, Office of The Surgeon General, (Jul 2008), Expert Clinical Laboratory Consultant: Justified transition from 2nd generation to 3rd generation methodology for HIV Force Health and briefed implications of current HIV screening technology on Force Health. DA transitioned

2008 COL Cordts, OTSG; (Jul 2008) HIV Rapid Test Brief, Support as Expert Consultant Laboratorian

2008 Nigerian Minister of Health (Sep 2008), USMHRP Program for COL Nelson Michael

2008 COL Thomas Logan, Acting Commander Center for Health Promotion and Preventative Medicine (Oct 2008) – HIV EPICON. Support as Expert Consultant Clinical Laboratorian and Task Team member.

2006 Tanzanian Minister of Health and Visiting Delegation (May 2006), USMHRP Program for COL Nelson Michael

2003 Prepared materials for Major General Martinez-Lopez US Army Medical Research and Materiel Command Briefing to General Kern, US Army Materiel Command. "Army Medical Science and Technology Initiatives in Advanced Biotechnology"

2002 Mr. Claude M. Bolton, Assistant Secretary of the Army for Acquisition, Logistics, and Technology, Lieutenant General John Caldwell, Director, Army Acquisitions Corps, Major General Martinez-Lopez, US Army Medical Research and Materiel Command. "DNA Microarry Technology; Process Overview for Malaria Oligonucleotide Mircroarrays; DNA Microarray Technology for Anitimalarial Drug Discovery and Development"

2002 Prepared materials for Congressional Briefing on successful transitions from Independent Laboratory Internal Research awards to Programmatic Funding for Dr A Michael Andrews II, Deputy Assistant Secretary of the Army for Research and Technology

2001 Brief to Genomics Sequencing Conference, Defense Advanced Research Projects Agency (DARPA). "Applications of Functional Genomics for Drug Discovery".

Diagnostic Referee

HVTN 505 Phase 2, randomized, placebo-controlled trail to evaluate the safety and effect on post-HIV acquisition viremia of a multiclade HIV-1 DNA plasmid vaccine followed by a multiclade HIV-1 recombinant adenoviral vector vaccine in HIV-1 uninfected, adenovirus 5 neutralizing antibody negative, circumcised men – in progress.

Academic/Teaching Experience

2002-2006 Uniform Services University of the Health Sciences, Medical Parasitology

1996-2001 Uniform Services University of the Health Sciences, MS-1 Diagnostic Parasitology and Medical Zoology, Laboratory Instructor, 1997-2001

1992-1995 University of North Carolina at Chapel Hill, School of Public Health, Introduction to Epidemiology; Molecular Biology

1988-1991 Duke University Medical School, Medical Parasitology

1988-1991 University of North Carolina School of Medicine, Medical Parasitology,

1987 University of North Carolina at Chapel Hill, School of Public Health, Bacteriology Laboratory Practice

Societies Membership

International Society for Environmental and Biological Repositories
International Society for Analytical Cytometry
Clinical Cytometry Society
American Society of Tropical Medicine and Hygiene
American Society of Microbiology
American Association for the Advancement of Science

Society Participation

Manuscript reviewer:

Transfusion
Blood
Journal Clinical Microbiology
Experimental Parasitology
American Journal Tropical Medicine and Hygiene
AIDS Research and Human Retroviruses
AIDS Research and Treatment
PLusOne
Journal of Virological Methods

Grant Reviewer

Global Aids Program, Office of Global AIDS Coordinator
World Health Organization
NIH Clinical Immunology Review Branch
NIH Minority Biomedical Research Support of Continuous Research Excellence
National Institute of Standards and Technology
North Carolina Center for Biotechnology

Publications

Jagodzinski LL, Manak MM, Hack HR, Liu Y, Peel SA. Performance Evaluation of a Laboratory Developed PCR Test for Quantitation of HIV-2 Viral RNA. 2020. PloS One. Feb 28;15(2):e0229424. doi: 10.1371/journal.pone.0229424. eCollection 2020

Crowell TA, Lawlor J, Lombardi K, Nowak RG, Hardick J, Odeyemi S, Kokogho A, Malia J, Stewart C, Robb ML, Baral SD, Adebajo S, Charurat ME, Ake JA, Peel SA, Gaydos CA; TRUST/RV368 Study Group. 2019. Anorectal and Urogenital Mycoplasma Genitalium in Nigerian Men who have Sex with Men and Transgender Women: Prevalence, Incidence, and Association with HIV. Sex Transm Dis. 2019 Dec 26. doi: 10.1097/OLQ.0000000000001105. [Epub ahead of print]

Manak MM, Jagodzinski LL, Shutt A, Malia JA, Leos M, Ouellette J, Akapirat S, Colby DL, Phanuphak N, Eller LA, Robb ML, de Souza M, Ananworanich J, Peel SA; RV254/SEARCH010 and the RV217 Study Teams. 2019. Decreased Seroreactivity in individuals initiating antiretroviral therapy during acute HIV infection. J Clin Microbiol. 2019 Sep 24;57(10). pii: e00757-19. doi: 10.1128/JCM.00757-19. Print 2019 Oct.

Kijak GH, Sander-Buell E, Pham P, Harbolick EA, Oroperz C, O'Sullivan AM, Bose M, Beckett CG, Milazzo M, Robb ML, Peel SA, Scott PT, Michael NL, Armstrong AW, Kim JH, Brett-Major DM, Tovanabutra S. 2019. Next-generation Sequencing of HIV-1 Single Genome Amplicons. *Biomol Detect and Quantif 17:100080* .

Jagodzinski LL, Manak MM, Hack HR, Liu Y, Malia JA, Freeman J, Phanuphak N, de Souza M, Kroon ED, Colby DJ, Chomchey N, Lally MA, Michael NL, Ananworanich J, Peel SA; RV254 SEARCH010 Study Team. 2019. Impact of Early Antiretroviral Therapy on Detection of Cell-Associated HIV-1 Nucleic Acid in Blood by the Roche COBAS TaqMan Test. J. Clin. Microbiol. Mar 6. pii: JCM.01922-18. doi: 10.1128/JCM.01922-18. [Epub ahead of print].

Manak MM, Hack HR, Shutt AL, Danboise BA, Jagodzinski LL, Peel SA. 2018. Stability of Human Immunodeficiency Virus Serological Markers in Samples Collected as HemaSpot and Whatma 903 Dried Blood Spots, *J. Clin. Microbiol*. Sep 25;56(10)

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Hakre S, Casimier RO, Danboise BA, Peel SA, Michael NL, Scott PT, Okulicz JF. 2017 Enhanced Sexually Transmitted Infection Screening for Mycoplasma Genitalium in Human Immunodeficiency Virus Infected US Air Force Personnel .*Clin Infect Dis*. 2017 Oct 16;65(9):1585-1588. doi: 10.1093/cid/cix555.

Okulicz JF, Beckett CG, Blaylock JM, Hakre S, Agan BK, Michael NL, Peel SA, Scott PT, Cervosky SB. 2017. Review of the U.S. military's human immunodeficiency virus program: a legacy of progress and a future of promise. *Med Sur Month Rep* Oct 24(9): 2-7.

Ake JA, Schuetz A, Pegu P, Wieczorek L, Eller MA, Kibuuka H, Sawe F, Maboko L, Polonis V, Karasavva N, Wiener D, Sekiziyivu A, Kosgei J, Missanga M, Kroidl A, Mann P, Ratto-Kim S, Eller LA, Earl P, Moss B, Dorsey-Spitz J, Mialazzo M, Ouedraogo GL, Rizvi F, Yan J, Khan Am, Peel S, Sardesai NY, Michael NL, Ngauy V, Marovich M, Robb ML. 2017. Safety and Immunogenicity of PENNVAX-G DNA, administered by Biojector 2000 or CELECTRA Electroporation Device with Modified Vaccinia Ankara-CMDR Boost. *J Infect Dis* Nov 27; 216(9): 1080-1090.

Hakre S, Jagodzinski LL, Liu Y, Pham PT, Kijak GH, Tovanabutra S, McCutchan FE, Scoville SL, Cersovsky SB, Michael NL, Scott PT, **Peel SA**. 2017 Characteristics of HIV-infected U.S. Army soldiers linked in molecular transmission clusters, 2001-2012 *PLoS One.* Jul 31;12(7):e0182376. doi: 10.1371/journal.pone.0182376. eCollection 2017.

Manak MM, Eller LA, Malia J, Jagodzinski LL, Trichavaroj R, Oundo J, Lueer C, Cham F, de Souza M, Michael NL, Robb ML, **Peel SA**. 2017 Identification of Acute HIV-1 Infection by Hologic Aptima HIV-1 RNA Qualitative Assay. *J Clin Microbiol*. Jul;55(7):2064-2073. doi: 10.1128/JCM.00431-17. Epub 2017 Apr 19.

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Ramadhani HO, Liu H, Nowak RG, Crowell TA, Ndomb T, Gaydos C, **Peel S**, Ndembi N, Baral SD, Ake J, Charurat ME; TRUST/RV368 Study Group. 2017 Sexual partner characteristics and incident rectal Neisseria gonorrhoeae and Chlamydia trachomatis infections among gay men and other men who have sex with men (MSM): a prospective cohort in Abuja and Lagos, Nigeria *Sex Transm Infect*. Aug;93(5):348-355. doi: 10.1136/sextrans-2016-052798. Epub 2017 Feb 24.

Njoku OS, Manak MM, O'Connell RJ, Shutt AL, Malia JA, Heipertz RA Jr, Tovanabutra S, Milazzo MJ, Akintunde GA, Alabi AS, Suleiman A, Ogundeji AA, Kene TS, Nelson R, Ayemoba OR, Singer DE, Robb ML, **Peel SA**, Michael NL. 2016 An Evaluation of Selected Populations for HIV-1 Vaccine Cohort Development in Nigeria *PLoS One.* Dec 9;11(12):e0166711. doi: 10.1371/journal.pone.0166711. eCollection 2016.

Keshinro B, Crowell TA, Nowak RG, Adebajo S, **Peel S**, Gaydos CA, Rodriguez-Hart C, Baral SD, Walsh MJ, Njoku OS, Odeyemi S, Ngo-Ndomb T, Blattner WA, Robb ML, Charurat ME, Ake J; TRUST/RV368 Study Group. 2016 High prevalence of HIV, chlamydia and gonorrhoea among men who have sex with men and transgender women attending trusted community centres in Abuja and Lagos, Nigeria. *J Int AIDS Soc*. Dec 7;19(1):21270. doi: 10.7448/IAS.19.1.21270. eCollection 2016.

Hannah WN Jr, Hakre S, Dawson P, Wu H, **Peel SA**, Michael NL, Scott PT, Okulicz JF. 2017 Clinical indicators associated with HIV acquisition in the United States Air Force. *AIDS Care*. Jun;29(6):724-728. doi: 10.1080/09540121.2016.1260086. Epub 2016 Nov 28.

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Manak MM, Hack HR, Nair SV, Worlock A, Malia JA, **Peel SA**, Jagodzinski LL. *J Clin Microbiol*. 2016 Evaluation of Hologic Aptima HIV-1 Quant Dx Assay on the Panther System on HIV Subtypes Oct;54(10):2575-81. doi: 10.1128/JCM.01350-16. Epub 2016 Aug 10

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Ndahimana JD, Riedel DJ, Mwumvaneza M, Sebuhoro D, Uwimbabazi JC, Kubwimana M, Mugabo J, Mulindabigwi A, Kirk C, Kanters S, Forrest JI, Jagodzinski LL, **Peel SA**, Ribakare M,

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EXHIBIT B

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Specimen Submission Guidelines

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Change Request

Name/Signature	Title	Date	Meaning/Reason
Jessica Polissedjian (JPOLISSEDJIAN)	QA Manager	21 May 2019, 01:14:02 PM	Approved

Collaboration

Name/Signature	Title	Date	Meaning/Reason
Joanna Freeman (JFREEMAN)		23 May 2019, 03:47:13 PM	Complete

preapproval

Name/Signature	Title	Date	Meaning/Reason
Jessica Polissedjian (JPOLISSEDJIAN)	QA Manager	30 May 2019, 12:50:07 PM	Complete

Originator Approval

Name/Signature	Title	Date	Meaning/Reason
Joanna Freeman (JFREEMAN)		30 May 2019, 01:04:14 PM	Approved

Supervisor Approval

Name/Signature	Title	Date	Meaning/Reason
Jennifer Malia (JMALIA)	ASST. CHIEF, DLDM	17 Jul 2019, 12:04:43 PM	Approved

QA approval

Name/Signature	Title	Date	Meaning/Reason
Jessica Polissedjian (JPOLISSEDJIAN)	QA Manager	22 Jul 2019, 12:33:41 PM	Approved

Lab Director Approval

Name/Signature	Title	Date	Meaning/Reason
Sheila Peel (SPEEL)	LAB DIRECTOR	23 Jul 2019, 01:52:31 PM	Approved

Training Coordinator

Name/Signature	Title	Date	Meaning/Reason
Jessica Polissedjian (JPOLISSEDJIAN)	QA Manager	23 Jul 2019, 04:07:53 PM	Approved

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Jessica Polissedjian (JPOLISSEDJIAN)	QA Manager	23 Jul 2019, 04:08:23 PM	Approved
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Walter Reed Army Institute of Research

DEPARTMENT OF LABORATORY DIAGNOSTICS AND MONITORING

SPECIMEN SUBMISSION GUIDELINES

Version: April 2019

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

TABLE OF CONTENTS

SUMMARY OF CHANGES

- June 2017
  - New HDRL web page is: http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory
  - Effective 12/1/2016, Geenius HIV 1/ 2 Supplemental Assay replaced Bio-Rad Multispot HIV 1/ 2 assay in the new US Army HIV Algorithm at the HIV Diagnostics and Reference Laboratory (HDRL). Sites will not see any change in the ordering process. On the "Result Report", the Multispot HIV 1/ 2 result was replaced with the Geenius HIV 1/ 2 results.
  - Effective 6/22/2017, SOP revised and reformatted. Significant changes included in the revision are: updated mission, inclusion of order of specimen draw instruction, addition of Test Specifications, reformatting and addition of Test Request forms to the SOP, molecular testing was broken out into three Test Request Forms based upon qualitative, quantitative and send out testing procedures, and addition of HIV test algorithms to the SOP.
- August 2017
  - Effective 8/18/2017, SOP revised. Significant change is addition of Appendix C, Packaging Instructions.
- April 2018
  - Effective 4/29/2018, SOP revised. Addition of *Mycoplasma genitalium* test.
- May 2018
  - Effective 5/2/2018, SOP revised. Updated the Director, US Military HIV Research Program to Robert Gramzinski, PhD.
  - Clarification of specimen storage section, Section 2.8.
- September 2018
  - Updated Assistant Laboratory Manager to CPT Jennifer Burns.
  - Addition of Appendix G, Verification Kit Instructions and Verification Kit Packing Instructions.
- April 2019
  - Changed the name of Appendix B3 from CONUS to RV351/CONUS
  - Removed specific package inserts from the test specifications found in Appendix A.

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Reference a complete list of the Summary of Changes on the HDRL website at:
http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HDRL Mission: The HIV Diagnostics and Reference Laboratory (HDRL), as part of the Department of Laboratory Diagnostics and Monitoring (DLDM), is dedicated to defining and executing state-of-art infectious pathogen diagnostics and monitoring in support of the Department of Defense and Department of Army personnel and their beneficiaries. HDRL assures the highest quality test results within the shortest feasible turnaround time.

1.0 GENERAL INFORMATION

1.1 LABORATORY SERVICES

The HIV Diagnostics and Reference Laboratory (HDRL), Department of Laboratory Diagnostics and Monitoring (DLDM), U.S. Military HIV Research Program (USMHRP), at the Walter Reed Army Institute of Research (WRAIR), is a Department of Defense – Clinical Laboratory Improvement Program (DoD-CLIP) and College of American Pathologists (CAP) accredited Reference Laboratory that offers testing to Department of Defense (DoD) Laboratories.

HDRL began its mission in 1986 as the HIV Diagnostics Laboratory, when Congress authorized creation of the USMHRP to protect U.S. troops and serve the global community by reducing the risk of Human Immunodeficiency Virus infection.

HDRL conducts standard retroviral serology testing and clinical (viral load) monitoring for both clinical care and in support of the USMHRP research protocols. HDRL conducts HIV screening of all U.S. Military Entrance Processing Command (USMEPCOM) applicants, confirmatory HIV testing for the Air Force and Navy and additional confirmatory Hepatitis B and Hepatitis C testing for Navy Service Members. The Laboratory also provides HIV-1 resistance genotyping services to all DoD HIV infected force members. In addition, HDRL conducts clinical *Mycoplasma genitalium* testing and is responsible for technical oversight of all Army retroviral diagnostics performed by independent government contractors.

NOTE: Only the U.S. Army European Command (USAREUR) and U.S. Army Central Command (CENTCOM) are authorized to use WRAIR/HDRL to meet HIV Surveillance (Force Screen) requirements. Non-USAREUR facilities must use Service-directed test facilities (contract laboratory); special requests for assistance must be coordinated with HDRL.

1.2 TEST MENU

Type	Tests Available	Test Specs
Serology	○ HIV Combo Ag/Ab EIA	Appendix A1
	○ HIV-1 Western Blot (WB) Supplemental	Appendix A2
	○ Geenius HIV 1/2 Supplemental	Appendix A3
	○ Hepatitis B Surface Antigen (HBsAg) Confirmatory Assay	Appendix A4
Molecular	○ HIV-1 Viral Load (COBAS AmpliPrep/ COBAS TaqMan)	Appendix A5
	○ HCV Viral Load (COBAS AmpliPrep/ COBAS TaqMan)	Appendix A6
	○ HIV-1 RNA Qualitative Assay (APTIMA)	Appendix A7
	○ HCV RNA Qualitative Assay (APTIMA)	Appendix A8
	○ HIV-1 Resistance Genotype	Appendix A9
	○ HIV-1 Integrase Genotype	Appendix A10
	○ HIV-1 Phenotype (sent out to reference laboratory)	Appendix A11
	○ HIV-1 Trofile (sent out to reference laboratory)	Appendix A12
	○ HIV-1 DNA PCR, HIV-2 DNA PCR	Appendix A13
	○ *Mycoplasma genitalium* (PANTHER)	Appendix A14

1.3 LABORATORY HOURS AND ADDRESS

Open Monday through Saturday from 0800 to 1830 EST for testing. Client Services available Monday through Friday from 0700 to 1600 EST at the number listed below. Closed Sundays and holidays.

SPECIMEN SUBMISSION SHIPPING ADDRESS
LABORATORY MAILING ADDRESS:

HIV Diagnostics and Reference Laboratory

Department of Laboratory Diagnostics and Monitoring

US HIV Military Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Phone: (301) 319-3123

Fax: (301) 319-3502

Websites

US Military HIV Research Program – http://www.hivresearch.org

HIV Diagnostics and Reference Laboratory – http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory

Reference the HDRL web page: – http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory for the latest Specimen Submission Guidelines, Test Descriptions, Testing Algorithms, Test Request and Point of Contact (POC) forms, and Accreditation Certificates (CAP and Clinical Laboratory Improvement Program [CLIP]).

1.4 POINTS OF CONTACT

Director, US Military HIV Research Program
Robert Gramzinski, PhD

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2.0 SPECIMEN COLLECTION, PROCESSING AND HANDLING

2.1 PATIENT PREPARATION

Verify patient identification and tests requested before specimen collection and follow local approved standard operating procedures.

2.2 ORDER OF DRAW

When multiple specimens are required, follow the proper order of draw (CLSI H3-A6, Section 8.10).

Order	Tube Type	Tube Stopper Color	Mix by Inverting
1	Blood Culture-SPS	Yellow	8-10 Times
2	**ACD***	Yellow	8-10 Times
3	Citrate	Light Blue	3-4 Times
4	**BD Vacutainer® SSTTM Gel Separator ***	Orange or Red/Black	5 Times
5	**Serum (Plastic Only)***	Red	5 Times
6	Heparin	Green	8-10 Times
7	BD Vacutainer® PST Gel Separator with Heparin	Light Green or Light Green/Black	8-10 Times
8	**EDTA* and PPT***	Lavender White	8-10 Times
9	Flouride (Glucose)	Grey	8-10 Times

** Signifies collection tubes used for tests identified in this manual*

2.3 REQUIREMENTS

NOTE: REFERENCE APPENDIX A, SPECIMEN SUBMISSION GUIDELINES FOR TEST SPECIFICATIONS AND INDIVIDUAL TEST DESCRIPTIONS, FOR SUBMISSION OF THE APPROPRIATE VOLUME AND TYPE OF SPECIMEN THAT IS REQUIRED OR TEST(S) MAY BE REJECTED.

WHOLE BLOOD

Collect whole blood according to instructions provided for the individual test referenced in Appendix A. Thoroughly mix blood tubes containing additives by gently inverting the tube as noted in order of draw above, and by referencing specific test specifications.

Maintain the specimen at room temperature before shipping to HDRL unless instructed otherwise by Test Specification requirements. **Never freeze whole blood** unless instructed to do so in accordance with a test's specimen collection and handling requirements (Appendix A). Do not place whole blood specimens in direct contact with ice/cool packs.

PLASMA

Plasma contains fibrinogen and other clotting factors when separated from the red blood cells. Evacuated tubes used to collect plasma specimens contain anticoagulants and, frequently, a preservative. The additive in each tube is specified on the label and tube stoppers are color-coded according to the additive present.

Consult the Test Specification requirements to determine the correct additive/tube to use. Tubes should be inverted 8-10 times immediately after collection, followed by **centrifugation within 4 hours of draw**. If specimen is transferred to a secondary tube, indicate the specimen type (plasma) on the plastic screw-cap vial for transport and on the corresponding test request form.

SERUM

HDRL recommends the use of serum separator collection tubes (SSTs) for most serological analyses. When using a serum separator tube, invert the tube gently 5 times. Further inversion may cause alterations in specimen integrity. **DO NOT centrifuge immediately after drawing blood.** Allow the blood to clot in an upright position for at least 30 minutes, but not longer than 2 hours before centrifugation. If specimen is transferred to a secondary tube, indicate that the specimen is serum on the plastic screw-cap vial for transport and on the corresponding test request form.

CENTRIFUGATION

Instructions for centrifugation of specimen collection tubes:

1	Draw 5 mL of whole blood for each 2 mL of serum or plasma required in an appropriate collection tube in appropriate order (section 2.2 Order of Draw).
2	If serum is required, allow the specimen to clot for at least 30 minutes, but no longer than 2 hours, in an upright position prior to centrifugation.
3	For **serum**, centrifuge within 2 hours of collection per manufacturer guidelines *unless otherwise specified for the individual test.**
4	For **plasma**, centrifuge within 4 hours of collection per manufacturer guidelines *unless otherwise specified for the individual test.**
5	Pipette the serum or plasma into a clean plastic screw-cap vial and attach the label. Do not transfer red cells to the vial.

*All non-gel blood collection tubes (including those that contain heparin, EDTA and non-gel serum tubes) can be centrifuged at ≤1300 RCF for 10 minutes. The BD Vacutainer® SST™ and PST™ gel tubes should be spun at room temperature at a speed of 1000 to 1300 RCF for 10 minutes in a swing bucket centrifuge or 15 minutes in a fixed-angle centrifuge. Information for conversions of RCF to RPM follows:

g Force (RCF) = $(rpm)^2 \times 1.118 \times 10^{-5} \times r$

RPM = $\sqrt{[RCF/(r \times 1.118)]} \times 1 \times 10^5$

URINE SPECIMENS

The Urine Specimen Transport Tube kit is used for the transport of male or female urine specimens requiring *Mycoplasma genitalium* testing. Ensure that the specimens are collected aseptically. After collecting urine in a preservative free urine collection cup, transfer 2 mLs of first-catch urine into the Aptima urine specimen transport tube within 24 hours of collection. Store and transport specimen at 2 – 30°C. Testing must be completed within 30 days of collection.

SWAB

The Aptima Unisex Swab Specimen Collection kit is used for collection of female endocervical or male urethral swab specimens as well as for the collection and transport of pharyngeal or rectal specimens requiring *Mycoplasma genitalium* testing. Ensure that the specimens are collected aseptically. Refer to the Hologic website for further collection information: https://www.hologic.com/sites/default/files/2018-01/AW-16968_001_01_0.pdf. After collection, break the swab tip off into the tube of media. Store and transport specimen at 2 – 30°C. Testing must be completed within 30 days of collection.

2.4 LABELING OF SPECIMENS

Verify identification once again post collection and before labeling the specimens.

Each submitted specimen must be labeled legibly with the following information to prevent test delay:

- Patient name
- Unique DoD number
- Social Security number (SSN) and family member prefix (FMP) (Required for inquiry of patient results/status in legacy LIMS)
- Date of birth and/or barcode written exactly as it appears on the test request form
- Date of collection/draw date
- Specimen type (e.g., serum, plasma, whole blood, urine, swab, etc.)

Failure to include required information on the specimen label may result in rejection of the specimen (section 2.6 Specimen Rejections).

2.5 SPECIMEN TEST REQUEST FORMS

Complete the appropriate HDRL Test Request Form (Appendix B) for each specimen:

- Serology Clinical Test Request Form (Appendix B1)
  - Suspicion of acute HIV infection: order the Acute HIV Algorithm (Appendix C) on the Serology Clinical Test Request Form. A 4th generation HIV Ag/Ab Combo test will be performed along with an HIV RNA Qualitative Test to assist with diagnosis of acute or primary HIV infection.
- HIV Verification Algorithm (Appendix D) Test Request Forms

  NOTE: non-CONUS (Appendix B2) and RV351/CONUS (Appendix B3) forms are different
- Molecular Aptima/Qualitative Test Request Form (Appendix B4)
  - Aptima HCV RNA Qualitative Assay is offered on the Molecular Test menu as a confirmatory test for the repeat reactive HCV EIA result. A quantitative HCV RNA test is available, if required, to assist with diagnosis and management of HCV infection.
- Molecular Viral Load (Quantitative)/Drug Resistance Test Request Form (Appendix B5)
- Molecular Send Out Test Request Form (Appendix B6)
- Vaccine Induced Sero-Reactivity Test Form (Appendix B7)
  - For Vaccine Induced Sero-Reactivity (VISR) individuals in whom Sero-Reactivity is suspected due to participation in a HIV vaccine trial, a complete HIV algorithm will be performed inclusive of DNA PCR (Additional testing may be performed if needed).
- Hepatitis B Surface Antigen Test Request Form (Appendix B8)
- *Mycoplasma genitalium* Test Request Form (Appendix B9)

All forms can be found on the HDRL website at:

http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory

NOTE: Enclose the appropriate Test Request Form(s) with patient specimen(s) in the shipment. Multiple tests may be requested, but each requested test requires a dedicated specimen.

Ensure that the specimens are shipped using federal, state, and international regulations as appropriate. See Appendix E, Packing Instructions, or HDRL website http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory

VERBAL TEST REQUESTS WILL ONLY BE ACCEPTED WHEN AN ADDITIONAL TEST IS REQUESTED POST-SUBMISSION ONLY IF FOLLOWED BY THE APPROPRIATE TEST REQUEST FORM WITHIN FIVE (5) BUSINESS DAYS.

NOTE: Do not send e-mails containing PHI to HDRL e-mail accounts that do not end in @mail.mil. When sending an e-mail that is inclusive of PHI, ensure that e-mail is transmitted encrypted.

NOTE: HDRL follows test algorithms (Appendix C and Appendix D). We may modify your request in order to run an initial screening test and then reflex, if indicated, for the test you requested.

2.6 SPECIMEN REJECTIONS

HDRL reserves the right to reject and discard specimens that:

- Do not meet the specimen collection and storage requirements specified on the appropriate Test Request Form(s)
- Contain the following errors:
  - Test Request Form errors include, but are not limited to:
    - Illegible information
    - Missing draw date
    - Missing family member prefix (FMP)
    - Missing/incomplete Social Security Number (SSN)
    - Missing/incomplete date of birth
    - Missing name of requesting physician and/or site
  - Specimen errors include, but are not limited to:
    - Provided specimen quantity not sufficient (QNS)
    - Duplicate specimen (same assay requested for same person within one 7-day period), unless authorized by the Laboratory Director
    - Illegible label
    - Incomplete information on label (at least two identifiers required per regulation)
    - Leaking/Cracked specimen tube
    - Incorrect specimen type
    - Specimens collected in expired collection tubes
    - Hemolyzed, contaminated, lipemic, or coagulated specimen
    - Package not in compliance with applicable federal and state shipping standards (such shipments will be rejected)
    - Specimens not shipped at specified shipping temperature
  - Mismatch errors between Test Request Form and specimen to include, but not limited to:
    - Discrepancy between specimen label and Test Request Form
    - Incorrect type of specimen for test requested
    - Missing specimen or Test Request Form

The submitting laboratory will be notified of any rejected specimen either by e-mail or telephone call, and will be sent a rejection report.

2.7 PACKAGING AND SHIPMENT OF SPECIMEN

Sites submitting specimens must comply with all applicable federal and state regulations concerning shipment for diagnostic specimens. The minimum requirements for packaging and shipping are:

1 Wrap all vials individually to avoid contact

2 Surround individually wrapped specimens with enough absorbent material to contain spillage

3 Package specimen in a water-tight primary and secondary container. Additional information can be found in Appendix E and on the HDRL website at: http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory.

4 Place request forms within the container but separate from the tubes

5 Label container and ship specimens according to applicable guidelines for diagnostic specimens

6 Mail to shipping address listed in section 1.3 Laboratory Hours and Address

7 **Fax/E-mail a FedEx/UPS tracking and/or invoice number to ensure all shipments sent to HDRL are received, IAW CAP GEN.40530 (REQUIRED OF SUBMITTING LABORATORY).**

NOTE: All personnel handling specimens for transport MUST be trained in safe handling practices and in decontamination procedures in case of spillage.

NOTE: If you would like your shipping boxes returned to your site, enclose a pre-paid FedEx/UPS shipping label or address slip with FedEx/UPS billing information and material to cover hazardous warning markings.

2.8 SPECIMEN STORAGE

To avoid hemolysis, separate serum from cells within 2 hours of draw and separate plasma within 4 hours of draw for EDTA or 2 hours of draw for PPT (refer to section 2.3 Requirements). Store specimen(s) according to requirements in the specimen submission guidelines (Appendix A).

Ship specimen(s) to HDRL in an appropriate shipping container, adhering to specimen temperature requirements listed on the Test Request Form(s) (Appendix B). If shipping specimen frozen, utilize an acceptable insulated container that will allow for 2+ lbs of dry ice (minimum) per day of transport. **Specimen(s) must arrive frozen.** HDRL also recommends the use of 6+lbs of dry ice during summer months to ensure acceptable specimen transport requirements are maintained, as well an anticipation of shipments that may be delayed due to issues with the carrier.

PPT tubes can be shipped at refrigerated temperature for delivery within 24 hours of collection.

Urine samples must be transferred to the Urine Specimen Transport tube within 24 hours of collection.

Store and transport *Mycoplasma genitalium* specimens at 2 – 30°C in the Aptima Unisex Swab Specimen Collection kit or Urine Specimen Transport tube.

NOTE: HDRL recommends using an additional 6 lbs. of dry ice in the event the package is delayed in transit to HDRL.

3.0 REPORTING OF RESULTS

HDRL will test all specimens submitted that adhere to specified Specimen Submission Guideline Test Specifications in an expeditious manner and in accordance with specified turnaround times.

HDRL generates hardcopy or electronic reports and transmits them via secured fax or encrypted e-mail to the designated Point of Contact (POC) at each submitting facility. On a limited basis, HDRL enters results directly in CHCS for specimens received through LIO. Result reports are also sent via secure file transfer to the Service-directed test facilities for the Army and Navy and directly to USMEPCOM. Due to the sensitive nature of our reports, only the designated POC (or alternate) can receive reports from HDRL. The facility POC is the sole manager of distribution of HDRL reports within that institution.

To designate a POC for results reporting, complete a Point of Contact Form – Results Reporting (Appendix F1). To designate a healthcare provider POC for notification and follow-up of positive patient test results, complete a Point of Contact Form – Notification and Follow-up Form (Appendix F2). Fax these forms to HDRL at 301-319-3502.

New sites MUST submit these forms before shipping specimens to HDRL for the first time. Use the same forms for updates/changes to these POCs. HDRL cannot/will not change or create POCs without these forms.

4.0 FOLLOW-UP PROCEDURES FOR POSITIVE RESULTS

Complete follow-up procedures are outlined in HDRL Standard Operating Procedure GEN 002. HDRL/WRAIR complies with AR 600-110 Army HIV Surveillance Program closely adhering to the following key points:

- Initial (first-time) HIV positive result for Active Duty Service members require the submission of a second specimen for independent verification of infection status. HDRL will coordinate with the site POC for shipment of a collection kit to the site as described below:
  - CONUS Active Duty Service members (Study ID RV351):
    - An RV351 HIV Verification Request Kit and Form (CONUS sites only) will be shipped to your site
    - The site must complete the accompanying Test Request Form and return the kit with specimens to HDRL according to the instructions provided (Appendix G)
  - OCONUS Active Duty Service members and other Service Components:
    - Complete the HIV Verification Algorithm Test Request Form found on the HDRL website
    - Ship the specimen to the address provided on the form
- If the original specimen and verification specimen are discordant, a third independent verification specimen will be required.
- Per AR 600-110, each site is required to have an appointed HIV Program Manager. This individual will serve as the POC for follow-up test coordination with HDRL.
- The identified Primary or Secondary POC will be notified by the HDRL or Army Public Health Command in accordance with HDRL SOP GEN 002.

5.0 SUPPORTING DOCUMENTS

Appendix A: Specimen Submission Guidelines (tests description and specification)
Appendix B: Test Request Forms
Appendix C: HIV Acute Infection Algorithm
Appendix D: HIV Testing Algorithm
Appendix E: Packaging Instructions
Appendix F: Point of Contact Forms
Appendix G: Verification Kit Instructions

NOTE: All documents (including CAP and DoD-CLIP certificates and Historical Changes to HDRL testing operations) are available online at:
http://www.hivresearch.org/hiv-diagnostics-and-reference-laboratory

Appendix A: Specimen Submission Guidelines (Tests description and specifications)

Appendix A1

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV Combo Ag/Ab EIA Test Specification

Test Name: HIV Combo Ag/Ab EIA				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
Enzyme immunoassay: The Genetics Systems HIV Combo Ag/AB EIA is based on the principle of the sandwich technique for the qualitative detection of HIV-1 p24 Antigen and detection of HIV-1 (Group M and O) and HIV-2 antibodies in human plasma. This 4th generation HIV test has significantly reduced the serological window of detection of HIV infection. Test employed: FDA-approved, commercially available test kit: Bio-Rad GS HIV Combo Ag/Ab EIA Reference Range: Not Detected	4 ml Serum or Plasma left on the SST/PPT tube or aliquoted in a screw top plastic vial Acceptable anticoagulants: EDTA, heparin, sodium citrate, CPD, CPDA-1, ACD	Shipping: Ambient (15 -30°C) Refrigerated (2-8°C) Frozen (-20°C or colder) Test must be performed within 2 days of draw if the specimen is stored and shipped at ambient temperature. Test must be performed within 7 days of draw if stored Refrigerated (2-8°C) and shipped with cold packs. Ship frozen if sample will not be received at HDRL within 48 hours. When shipping frozen, use 2+ lbs. dry ice per day of transport. Shipping on 6 lbs. additional dry ice recommended in case of shipment delay.	FDA approved for Screening for HIV-1 p24 Antigen and antibodies to HIV-1 (group O & M) and HIV-2.	5 business days (Clinical, Force Testing)

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HIV Diagnostics and Reference Laboratory
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Appendix A2

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 Western Blot (WB) Supplemental Test Specification

Test Name: HIV-1 Western Blot (WB)				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
In vitro qualitative assay for detection and identification of antibodies to HIV-1 in human serum and plasma. Test employed: FDA-approved, commercially available Western Blot Kit: Bio-Rad GS HIV-1 Western Blot. Reference Range: Negative	1 ml Serum or Plasma Acceptable anticoagulants: EDTA, heparin, sodium citrate, CPDA-1, ACD	Shipping: Ambient (15-37°C) Refrigerated (2-8°C) Frozen (-20°C) Test must be performed within 7 days of draw if shipped with cold packs or ambient temperature. Ship frozen if sample will not be received at HDRL within 48 hours. When shipping frozen, use 2+ lbs. dry ice per day of transport. Shipping on 6 lbs. additional dry ice recommended in case of shipment delay.	FDA approved as Supplemental Diagnostic test for confirmatory testing for HIV-1 antibodies	5 business days (Clinical, Force Testing)
Test performed on HIV EIA repeatedly reactive specimens per Army HIV Diagnostic Algorithm.				

Shipping Address: 9100 Brookville Road, BLDG 508, Silver Spring, MD 20910
• Tel: 301-319-3123 • Fax: 301-319-3502

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Geenius HIV 1/2 Supplemental Test Specification

Test Name: Geenius HIV-1/HIV-2 Supplemental Assay				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
Moderate complexity *in vitro* qualitative assay to aid in diagnosis of infection with HIV-1 and/or HIV-2 in fresh human serum and plasma. Test employed: FDA-approved, commercially available kit from Bio-Rad: Geenius HIV-1/2 Supplemental Assay. Reference Range: Negative	1 ml Serum or Plasma Acceptable anticoagulants: EDTA, sodium heparin and sodium citrate.	Shipping: Ambient (18-30°C) Refrigerated (2-8°C) Frozen (-20°C) Test must be performed within 48 hours of collection on ambient specimens and within 7 days of collection on refrigerated specimens. If sample will not be received at HDRL for testing within 48 hours of collection, freeze serum/plasma at -20°C. When shipping frozen, use 2+ lbs. dry ice per day of transport. Shipping with 6 lbs. of additional dry ice in situations where shipping delays might be experienced.	FDA approved as a supplemental test to aid in diagnosis of infection with HIV-1 and/or HIV-2	5 business days (Clinical, Force Testing)
Test performed on HIV repeatedly reactive specimens per Army HIV Diagnostic Algorithm.				

Shipping Address: 9100 Brookville Road, BLDG 508, Silver Spring, MD 20910
• Tel: 301-319-3123 • Fax: 301-319-3502

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Hepatitis B Surface Antigen (HBsAg) Confirmatory Assay Test Specification

Test Name: Hepatitis B Surface Antigen (HBsAg) Confirmatory Assay				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
The HBsAg Confirmatory Assay 3.0 is a qualitative assay intended for the confirmation of HBsAg repeatedly reactive specimens detected in the HBsAg EIA 3.0. Test employed: licensed commercially available: Bio-Rad GS HBsAg Confirmatory Assay 3.0 Reference Range: Negative	3 ml Serum or Plasma Acceptable anticoagulants: EDTA, heparin, sodium citrate, CPDA-1, ACD	Shipping: Ambient (15-30°C) Refrigerated (2-8°C) Frozen (-20°C) Test must be performed within 7 days of draw if shipped with cold packs or ambient temperature. Ship frozen if sample will not be received at HDRL within 7 days. When shipping frozen, use 2+ lbs. dry ice per day of transport. Shipping on 6 lbs. additional dry ice recommended in case of shipment delay.	HBsAg Confirmatory Assay 3.0 is FDA approved as a neutralization procedure for confirmatory testing of repeatedly reactive HBsAg EIA samples.	5 business days
Test performed on HBsAg EIA repeatedly reactive specimens per CDC guidelines				

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
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HIV-1 Viral Load (COBAS AmpliPrep/COBAS TaqMan) Test Specification

Test Name: HIV-1 RNA Real-Time PCR (Viral Load)				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
In vitro nucleic acid amplification test for quantitation of RNA from patients infected with HIV-1 (Group M, subtypes A-H). Intended for use in conjunction with clinical presentation and other laboratory markers. Test employed: FDA-approved, commercially available test kit from Roche: COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test; analytical measurement range: 20-10,000,000 copies/ml	EDTA (lavender top) Plasma only, minimum volume of 3 ml Centrifuge at room temperature at 800 – 1600 x g for 20 minutes within 4 hours of blood collection. Store refrigerated (2-8°C) for overnight or same day delivery.	Ship frozen if transport will take longer than same day or overnight. EDTA Plasma: Store plasma frozen (-70°C or colder). When shipping frozen, use 2+ lbs. dry ice per day of transport. Recommended: Ship on 6 lbs. dry ice in case of shipment delay.	FDA approved for patient management (NOT for diagnostic use)	5 business days

Shipping Address: 9100 Brookville Road, BLDG 508, Silver Spring, MD 20910
• Tel: 301-319-3123 • Fax: 301-319-3502

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HCV Viral Load (COBAS AmpliPrep/COBAS TaqMan) Test Specification

Test Name: HCV RNA Real-Time PCR (Viral Load)				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
In vitro nucleic acid amplification test for quantitation of RNA from patients infected with HCV (Genotype 1-6). Intended for use in conjunction with clinical presentation and other laboratory markers. Test employed: FDA-approved, commercially available test kit from Roche: COBAS AmpliPrep/ COBAS TaqMan HCV Test; analytical measurement range: 15-100,000,000 IU/ml	EDTA (lavender top) Plasma only, minimum volume of 3 ml Centrifuge at room temperature at 800-1600 x g for 20 minutes within 4 hours of blood collection. Store refrigerated (2-8°C) for overnight or same day delivery.	Ship frozen if transport will take longer than same day or overnight. EDTA Plasma: Store plasma frozen (-70°C or colder). When shipping frozen, use 2+ lbs. dry ice per day of transport. Recommended: Ship on 6 lbs. dry ice in case of shipment delay.	FDA approved for patient management.	5 business days

Shipping Address: 9100 Brookville Road, BLDG 508, Silver Spring, MD 20910
• Tel: 301-319-3123 • Fax: 301-319-3502

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 RNA Qualitative Assay (APTIMA) Test Specification

Test Name: APTIMA HIV-1 RNA Qualitative Assay				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
In vitro nucleic acid assay system for detection of HIV-1 in human plasma. Intended for use as an aid in diagnosis of HIV-1 infection, including acute or primary infection. Presence of HIV-1 RNA in the plasma of patients without antibodies to HIV-1 is indicative of acute or primary HIV-1 infection. May also be used as an additional test, when it is reactive, to confirm HIV-1 infection in an individual whose specimen is repeatedly reactive for HIV-1 antibodies. Test employed: FDA-approved, commercially available test kit: Hologic Aptima HIV-1 RNA Qualitative Assay. Reference Range: Not Detected	Minimum of 3 ml plasma (frozen) or serum Centrifuge at room temperature according to tube manufacturer guidelines within separation times below: PPT Tubes: Centrifuge immediately or within 2 hours of collection at 1100 x g for 10 minutes minimum. EDTA Plasma: Store blood at 25°C until centrifuged. Centrifuge at ≤1300 x g for 10 minutes within 4 hours of blood collection. Ship frozen if transport longer than overnight delivery. Serum Tubes: Allow blood to clot in upright position for 30-60 minutes before centrifugation. If transferring to secondary tube, indicate "serum" on plastic screw-cap tube for transport.	Ship frozen (-20° or colder) if transport longer than same day or overnight delivery. Store refrigerated (2-8°C) for same day or overnight delivery. If transport longer than overnight, aliquot plasma, freeze at -70°C, then ship frozen on dry ice. Store plasma frozen (-70° or colder). Use 2+ lbs. dry ice per day of transport. Recommended: Ship on 6 lbs. dry ice in case of shipment delay.	FDA approved for molecular diagnosis of acute and primary HIV-1 Not intended for use in screening blood or plasma donors	5 business days

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HCV RNA Qualitative Assay (APTIMA) Test Specification

Test Name: APTIMA HCV RNA Qualitative Assay				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
In vitro nucleic acid assay system for detection of HCV in human plasma. Intended for use as an aid in diagnosis of HCV infection, including acute or primary infection. Is used as a confirmatory test to confirm HCV infection in an individual whose specimen is repeatedly reactive for HCV antibodies. Qualitative HCV RNA testing may be used for identifying the endpoint of infection following antiviral treatment. Test employed: FDA-approved, commercially available test kit: Hologic Aptima HCV RNA Qualitative Assay. Reference Range: Not Detected	Minimum of 3 ml plasma (frozen) or serum Centrifuge at room temperature according to tube manufacturer guidelines within separation times below: PPT Tubes: Centrifuge immediately or within 2 hours of collection at 1100 x g for 10 minutes minimum. EDTA Plasma: Store blood at 25°C until centrifuged. Centrifuge at 1300 x g for 10 minutes within 24 hours of blood collection. Ship frozen if transport longer than overnight delivery. Serum Tubes: Allow blood to clot in upright position for 30-60 minutes before centrifugation. If transferring to secondary tube, indicate "serum" on plastic screw-cap tube for transport.	Ship frozen (-20° or colder) if transport longer than same day or overnight delivery. Store refrigerated (2-8°C) for same day or overnight delivery. If transport longer than overnight, aliquot plasma, freeze at -70°C, then ship frozen on dry ice. Store plasma frozen (-70° or colder). Use 2+ lbs. dry ice per day of transport. Recommended: Ship on 6 lbs. dry ice in case of shipment delay.	FDA approved for molecular diagnosis of acute and primary HCV infection. Not intended for use in screening blood or plasma donors.	5 business days

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 Resistance Genotype Test Specification

Test Name: HIV-1 Genotype				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
Intended for use in detecting genomic mutations within protease and reverse transcriptase regions of HIV-1 that confer resistance to antiretroviral drugs. Intended for use in conjunction with clinical presentation and other laboratory markers as an indicator of disease progression and as an assay to monitor or assess viral response to antiretroviral treatment. The test is available for all patients who are: (1) initiating drug therapy; (2) not responding to antiretroviral drug therapy (low viral RNA level at 1,000 to 3,000 copies/ml); or (3) failing their antiretroviral regimen. Test employed: FDA-approved, commercially available test kit from Abbott Viroseq HIV-1 Genotype Assay.	Two (2) vials of non-heparinized plasma at 1 ml per tube Centrifuge at room temperature at 800-1600 x g for 20 minutes within separation times below: PPT Tubes: Centrifuge immediately or within 2 hours of collection. Store at ambient temperature for overnight delivery, or transfer to sterile 2.0 ml polypropylene screw-cap tubes at 1 ml per tube and store at -60 to -80°C. EDTA Plasma: Store blood at 25°C until centrifuged. Centrifuge within 4 hours of collection. Aliquot EDTA plasma to sterile 2.0 ml polypropylene screw-cap tubes at 1 ml per tube. Store at -70°C. **Please note:** Patients presently on antiretroviral drug therapy should still be on their drug regimen when specimen is collected.	PPT Tubes: Store spun tubes refrigerated (2-8°C) for overnight or same day delivery. If transport longer than overnight or same day, aliquot plasma, freeze at -70°C, then ship frozen. Store plasma frozen (-70°C or colder). EDTA Plasma: Store refrigerated (2-8°C) for overnight or same day delivery. If transport longer than overnight or same day, aliquot plasma, freeze at -70°C, then ship frozen. Store plasma frozen (-70°C or colder). Use 2 lbs. dry ice per day of transport. Recommended: Ship on 6 lbs dry ice in case of shipment delay.	FDA approved for clinical monitoring of HIV-infected individuals	15 business days Due to low volume of tests requested, samples are batched for testing.

Please note:
1. Viral load MUST BE ≥ 2,000 copies/ml and result must have been obtained within the past 30 days. Viroseq HIV-1 Genotype testing can be performed if viral load is between 1,000 to 2,000 copies /ml, but a resistance profile may not be generated.
2. When requesting HIV-1 Genotype, requesting lab must provide most recent Viral Load result on request form at time of submission.
3. If the patient has not had a Viral Load determination within the past 30 days, request a HIV-1 Viral Load along with the HIV-1 Genotype request.
4. Any specimen without a Viral Load reported (or a Viral Load requested) on the request form will need resolution and may affect Turn Around Time.
5. Duplicate specimens will be discarded.

Appendix A10

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 Integrase Genotype Test Specification

Test Name: HIV-1 Integrase Genotype				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time**
Intended for use in detecting genomic mutations in Integrase region of HIV-1 conferring resistance to specific types of antiretroviral drugs. Intended for use in conjunction with clinical presentation and other laboratory markers as an indicator of disease progression and as an assay to monitor or assess viral response to antiretroviral treatment The test is available for all patients who are: (1) initiating drug therapy; (2) not responding to antiretroviral drug therapy (low viral RNA level at 1,000 to 3,000 copies/ml); or (3) failing their antiretroviral regimen. Not FDA approved, Laboratory Developed Test using commercially available test kit from Abbott Viroseq HIV-1 Integrase Genotype.	Two (2) vials of non-heparinized plasma at 1 ml per tube Centrifuge at room temperature at 800-1600 x g for 20 minutes within separation times below: PPT Tubes: Centrifuge immediately or within 2 hours of collection. Store at ambient temperature for overnight delivery, or transfer to sterile 2.0 ml polypropylene screw-cap tubes at 1.0 ml per tube and store at -60 to -80°C. EDTA Plasma: Store blood at 25°C until centrifuged. Centrifuge within 4 hours of collection. Aliquot EDTA plasma to sterile 2.0 ml polypropylene screw cap tubes at 1.0 ml per tube. Store at -70°C. **Please note:** Patients presently on antiretroviral drug therapy should still be on their drug regimen when specimen is collected.	PPT Tubes: Store spun tubes refrigerated (2-8°C) for overnight or same day delivery. If transport longer than overnight or same day, aliquot plasma, freeze at -70°C, then ship frozen. Store plasma frozen (-70°C or colder). EDTA Plasma: Store refrigerated (2-8°C) for overnight or same day delivery. If transport longer than overnight or same day, aliquot plasma, freeze at -70°C, then ship frozen. Store plasma frozen (-70°C or colder). Use 2 lbs. dry ice per day of transport. Recommended: Ship on 6 lbs dry ice in case of shipment delay.	This test was developed and its performance characteristics determined by HDRL. It has not been cleared or approved by the US Food and Drug Administration.	15 business days after receipt at HDRL. Due to low volume of tests requested, samples are batched for testing.

Please note:

1. Viral load MUST BE ≥ 2,000 copies/ml and result must have been obtained within the past 30 days. Viroseq HIV-1 Integrase Genotype testing can be performed if viral load is between 1,000 to 2,000 copies /ml, but a resistance profile may not be generated.
2. When requesting HIV-1 Integrase Genotype, requesting lab must provide most recent Viral Load result on request form at time of submission.
3. If the patient has not had a Viral Load determination within the past 30 days, request a HIV-1 Viral Load along with the HIV-1 Integrase Genotype request.
4. Any specimen without a Viral Load reported (or a Viral Load requested) on the request form will need resolution and may affect Turn Around Time.
5. HIV-1 Resistance Genotype should be ordered along with HIV-1 Integrase Genotype. Samples that do not have HIV-1 Resistance Genotype ordered on request form will need resolution and may affect Turn Around Time.
6. Duplicate specimens will be discarded.
7. Treatment Decision should be made in consideration of all relevant clinical and laboratory findings and the prescribing information of the drug in question.

Appendix A11

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 Phenotype (sent out to reference laboratory) Test Specification

Test Name: HIV-1 Phenotype				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
To aid clinicians in selection of most effective antiretroviral regimens for patients who are highly resistant to antiretroviral agents due to long-term therapy. Sent out to reference lab (i.e. Monogram Biosciences).	Minimum of 4 ml non-heparinized plasma from either PPT or EDTA tubes. Centrifuge at room temperature at 1000 – 1200 x g for 10 – 15 minutes within separation times below: PPT Tubes: Centrifuge immediately or within 2 hours of collection. Separate plasma. Aliquot into sterile 2 ml polypropylene screw-cap tubes at 1 ml per tube. Store frozen at -20 to -80°C until shipped. EDTA Plasma: Centrifuge within 4 hours of collection. Separate plasma. Aliquot into sterile 2 ml polypropylene screw cap tubes at 1 ml per tube. Store frozen at -20 to -80°C until shipped. **Please note:** Patients presently on antiretroviral drug therapy should still be on their drug regimen when blood specimen collected.	Frozen Use 2 lbs. of dry ice per day of transport. Recommended: Ship on 6 lbs dry ice in case of shipment delay.	Non FDA approved Used to inform selection of therapeutic regimens for patients failing therapy.	25 business days

Please note:
1. HIV-1 Genotype results should indicate resistance to a majority of antiretroviral drugs.
2. **Patient Viral Load must be ≥ 500 copies/ml at time of test.** If Viral Load results are not current within the past 30 days, request an HIV-1 Viral Load on the test request form in addition to the HIV-1 Phenotype request. **HDRL will not forward specimens for HIV-1 Phenotyping with Viral Loads < 500 copies/ml, or if HIV-1 genotype does not indicate antiretroviral resistance.**

Appendix A12

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 Trofile (sent out to reference laboratory) Test Specification

Test Name: HIV-1 Trofile				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
To determine HIV-1 viral tropism (the means of entry into cells used by a given strain of HIV, specifically which co-receptor the virus is using to enter healthy CD4+ T-cells—CCR5, CXCR4, or both). Sent out to reference lab (i.e. Monogram BioSciences).	Minimum of 4 ml plasma from 2 PPT or EDTA tubes. Centrifuge at room temperature at 1000-1200 x g for 10-15 minutes within separation times below: PPT Tubes: Centrifuge immediately or within 30 minutes of collection. Separate plasma. Aliquot into 2 sterile 2 ml polypropylene screw-cap tubes. Store frozen at -20°C until shipped. EDTA Plasma: Centrifuge immediately or within 30 minutes of collection. Separate plasma. Aliquot into sterile 2 ml polypropylene screw-cap tubes. Store frozen at -20°C until shipped.	Frozen Use 2 lbs. of dry ice per day of transport. Recommended: Ship on 6 lbs dry ice in case of shipment delay.	Non FDA approved Used in conjunction with other diagnostic test results to identify the most appropriate therapy and to select patients who may benefit from CCR5-antagonist therapy.	25 business days
Please note: **Patient Viral Load must be ≥ 1000 copies/ml at time of test.** If Viral Load results are not current **within the past 14 days**, request an HIV-1 Viral Load on the test request form in addition to the HIV-1 Trofile request. **HDRL will not forward specimens for HIV-1 Trofile with Viral Loads < 1000 copies/ml.**				

Appendix A13

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV-1 DNA PCR, HIV-2 DNA PCR Test Specification

Test Name: HIV-1 DNA PCR / HIV-2 DNA PCR				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
HIV-1 DNA PCR: Qualitative HIV-1 DNA test for detection of HIV-1 infection in infants up to 18 months of age, and detection of HIV-1 proviral DNA. HIV-2 DNA PCR: Qualitative DNA test to distinguish between HIV-1 and HIV-2 infection.	3 ml (0.5 ml minimum) whole blood in EDTA (lavender top) tubes Store at room temperature (15-30°C) for overnight or same day delivery.	Ship ambient within 24 hours of collection.	Not FDA approved HIV-1 DNA PCR intended for use in screening of infants 18 months of age or less, born to HIV-1 infected mothers. HIV-2 DNA PCR intended use for follow-up evaluation of negative results on confirmatory HIV-1 RNA testing, when clinically indicated.	10 business days

Please note:

1. Maternal antibodies may persist for the first 18 months of life, confounding diagnosis in the infant; however, maternal antibodies do not interfere in the HIV-1 DNA test.
2. This test may be used to detect HIV-1 in patients with acute infection prior to seroconversion (antibody formation), as well as in patients with agammaglobulinemia.
3. It is recommended that positive results be confirmed on two separate blood samples with one or a combination of virus-specific tests. Repeatedly reactive HIV-1 EIA results with supplemental confirmatory test are required to confirm the diagnosis HIV-1 infection.
4. HIV-2 DNA PCR is a highly sensitive and specific method to detect the presence of HIV-2 proviral DNA in specimens.
5. The diagnosis of HIV-2 infection should not rely solely upon the result of a PCR assay. A negative PCR result indicates the absence of HIV-2 provial DNA at detectable levels in the sample and does not exclude diagnosis of disease.

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SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

***Mycoplasma genitalium* Assay Test Specification**

Test Name: *Mycoplasma genitalium* Assay for Hologic PANTHER				
Clinical Significance	**Specimen Requirements**	**Transport/Storage Temperature**	**Test Approved For**	**Turn Around Time (After Receipt at HDRL)**
The MGen Assay for the Panther system is an automated *in vitro* target amplification nucleic acid probe assay that uses target capture for the detection of *Mycoplasma genitalium*. Test employed: licensed commercially available: Hologic Panther System Reference Range: Negative	Hologic Aptima Unisex Swab Specimen Collection Kit for Pharyngeal, Rectal, and Endocervical Swabs Hologic Aptima Urine Specimen Collection Kit (filled between the black lines within 24 hours of collection)	Shipping: Ambient (15-30°C) Refrigerated (2-8°C) Test must be performed within 30 days of collection.	This assay is not FDA cleared or approved. HIV Diagnostic and Reference Laboratory has validated this Laboratory Developed Assay for clinical research use.	5 business days
Please note: This test was developed and its performance characteristics determined by HDRL. It has not been cleared or approved by the US Food and Drug Administration (US FDA). Treatment decisions should be made in consideration of all relevant clinical and laboratory findings.				

Shipping Address: 9100 Brookville Road, BLDG 508, Silver Spring, MD 20910
• Tel: 301-319-3123 • Fax: 301-319-3502

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix B: Test Request Forms

Appendix B1

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Serology Clinical Test Request Form

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **HIV Algorithm** ☐ **Acute HIV Algorithm**	☐ 4 ml serum (SST Tubes) or ☐ 4 ml plasma (PPT preferred, EDTA, Na Heparin, Na Citrate, CPDA and ACD-1 plasma is acceptable.)	**SST Tubes** – Invert 5X and allow to clot for 30 min (no more than 2 hrs) post-collection. Centrifuge 10 minutes at 1000-1300 RCF in a swing bucket centrifuge. **NOTE:** Tubes MUST be allowed to clot for 30 minutes. **PPT tubes** – Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge in swing-out rotor centrifuge at 1100 RCF for a minimum of 10 min. Freeze plasma aliquot at -20°C.	☐ **Ambient 15-30°C** – SST tube must be received at HDRL within 2 days of collection. ☐ **Refrigerated 2-8°C** – SST tube must be immediately stored and shipped in cold box with ice packs and received at HDRL within 2-7 days of collection. ☐ **Frozen -20°C** – Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 7 days of collection.

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR SER Version: 06/2017

Appendix B2

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

HIV Verification Algorithm Test Request Form (non-CONUS)

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **HIV Algorithm**	☐ 4 ml serum (SST Tubes) or ☐ 4 ml plasma (PPT preferred. EDTA, Na Heparin, Na Citrate, CPDA and ACD-1 plasma is acceptable.)	**SST Tubes** – Invert 5X and allow to clot for 30 min (no more than 2 hrs) post-collection. Centrifuge 10 minutes at 1000-1300 RCF in a swing bucket centrifuge. **NOTE:** Tubes MUST be allowed to clot for 30 minutes. **PPT tubes** – Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge in swing-out rotor centrifuge at 1100 RCF for a minimum of 10 min. Freeze plasma aliquot at -20°C.	☐ **Ambient 15-30°C** – SST tube must be received at HDRL within 2 days of collection. ☐ **Refrigerated 2-8°C** – SST tube must be immediately stored and shipped in cold box with ice packs and received at HDRL within 2-7 days of collection. ☐ **Frozen -20°C** – Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 7 days of collection.

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR HIVVER Version 06/2017

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix B3 – RV351/CONUS

HIV DIAGNOSTICS AND REFERENCE LABORATORY
13 Taft Ct. Suite 100 Rockville, MD 20850

HIV Verification Algorithm Test Request Form

TESTS	SPECIMEN REQUIREMENT	DRAW TUBE
☐ **HIV Algorithm**	4 ml plasma (Cold Pack)	PPT

SHIP FROZEN PLASMA IF SAMPLE WILL NOT BE RECEIVED AT HDRL WITHIN 72 HOURS.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient Stamp must include: Full Name*, FMP*/SSN*, DOB*	**POC*** _____ **Physician Name*** _____ _____ **Clinic / Center*** _____ _____ **Center Address*** _____ _____ _____ _____
Specimen Draw Date / Time*: _____ Ship Date: _____ Sample Storage (circle): **Frozen / Refrig / Ambient** Sample Shipping (circle): **Dry Ice / Cold Pack**	Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

***Required**

PROCESSING LAB (For internal use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED/INITIALS

TUBES DRAWN	SPECIMEN REQUIREMENT	INSTRUCTIONS
☐ **4 PPT s**	Aliquot PPL into NINE (9) cryovials - 2, 1.0 mL each - 2, 0.5 mL each - 1, 2mL - 2, 1.20 mL each - 1, 2 mL - 2, remaining volume	Freeze at -80°C or lower Forward one vial of plasma at 1 ml to HDRL for confirmatory testing
☐ **2 CPTs**	Collect Cell Pellets and store into SEVEN (7) cryovials - 2, 5 million cells each - 5, 1 million cells each	Freeze at -80°C or lower

Form # TR VA Version May 2014

Appendix B4

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Molecular Aptima/Qualitative Test Request Form

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **APTIMA HIV-1 RNA Qualitative** ☐ **APTIMA HCV RNA Qualitative**	☐ 3 ml serum (SST Tubes)	**SST Tubes:** Invert 5X and allow to clot for 30 min (no more than 2 hrs) post-collection. Centrifuge 10 minutes at 1000-1300 RCF (g) in a swing bucket centrifuge. **NOTE:** Tubes MUST be allowed to clot for 30 minutes.	☐ **Refrigerated 2-8°C** – SST tube must be immediately stored and shipped in cold box with ice packs and received at HDRL within 24 hours of collection. ☐ **Frozen -20°C** – Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED:** Ship on 6 lbs. dry ice in case of shipment delay.
	☐ 3 ml plasma (PPT preferred, EDTA)	**PPT Tubes:** Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge ≤1300 RCF for 10 minutes. Freeze plasma aliquot at -20°C. **EDTA:** Store blood at 25°C until centrifuged. Centrifuge ≤1300 RCF for 10 minutes within 4 hours of blood collection. Ship frozen if transport longer than overnight delivery.	

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR Aptima Version 04/2018

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix B5

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Molecular Viral Load (Quantitative)/Drug Resistance Test Request Form

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **HIV-1 Viral Load** ☐ **HCV Viral Load**	☐ 3 ml plasma (EDTA only)	**EDTA:** Store blood at 25°C until centrifuged. Centrifuge ≤1300 RCF for 20 minutes within 4 hours of blood collection. Store refrigerated (2-8°C) overnight or for same day delivery.	☐ **Frozen -70°C** - Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED:** Ship on 6 lbs. dry ice in case of shipment delay.
☐ **HIV-1 Resistance Genotyping** ☐ **HIV-1 Integrase Genotyping**	☐ 2 ml plasma (EDTA or PPT) Viral load **MUST BE ≥ 2000** Copies/ml and result must have been obtained within the past 30 days.	**PPT Tubes:** Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge ≤1300 RCF for 10 minutes. Freeze plasma aliquot at -60 to -80°C. **EDTA:** Store blood at 25°C until centrifuged. Centrifuge ≤1300 RCF for 10 minutes within 4 hours of blood collection. Store at -70°C. Viral Load_____ Date Performed_____	☐ **Refrigerated 2-8°C** - Must be stored at 2-8°C post-centrifugation, shipped in cold box with ice packs and received at HDRL within 24 hours of collection. ☐ **Frozen** - Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED:** Ship on 6 lbs. dry ice in case of shipment delay.

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name**_____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name_____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR VL/DR Version 06/2017

Appendix B6

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Molecular Send Out Test Request Form

Test Requested (Check one)	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **HIV-1 Phenosense** **Note:** Patients on antiretroviral drug therapy should remain on drug regimen when blood collected.	☐ 4 ml plasma (EDTA or PPT) Viral load MUST BE ≥ 500 Copies/ml and result must have been obtained within the past 30 days.	**PPT Tubes:** Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge 1000-1200 X g for 10-15 minutes. Freeze plasma aliquot at -20 to -80°C. **EDTA:** Store blood at 25°C until centrifuged. Centrifuge 1000-1200 X g for 10-15 minutes within 4 hours of blood collection. Store at -20 to -80°C. Viral Load_____ Date Performed_____	☐ **Frozen** - Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED:** Ship on 6 lbs. dry ice in case of shipment delay.
☐ **HIV-1 Trofile**	☐ 4 ml plasma (EDTA or PPT) Viral load MUST BE ≥ 1000 Copies/ml and result must have been obtained within the past 14 days.	**PPT Tubes:** Invert 8-10X. Spin tubes within 30 minutes of collection. Centrifuge 1000-1200 X g for 10-15 minutes. Freeze plasma aliquot at -20°C. **EDTA:** Store blood at 25°C until centrifuged. Centrifuge 1000-1200 X g for 10-15 minutes within 30 minutes of blood collection. Store at -20°C. Viral Load_____ Date Performed_____	☐ **Frozen** - Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED:** Ship on 6 lbs. dry ice in case of shipment delay.
☐ **HIV-1 DNA PCR** ☐ **HIV-2 DNA PCR**	☐ 3 ml whole blood (EDTA only)	**EDTA:** Store at room temperature for overnight or same day delivery.	☐ **Ambient** - Ship ambient within 24 hours of collection.

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)

BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR MSO Version 06/2017

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Vaccine Induced Sero-Reactivity Test Request Form

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **VISR Algorithm**	☐ 3 ml serum (SST Tubes) or ☐ 3 ml plasma (PPT preferred) or ☐ 15 ml whole blood (3 x 5ml EDTA tubes)	**SST Tubes** – Invert 5X and allow to clot for 30 min (no more than 2 hrs) post-collection. Centrifuge 10 minutes at 1000-1300 RCF in a swing bucket centrifuge. **NOTE:** Tubes MUST be allowed to clot for 30 minutes. **PPT tubes** – Invert 8-10X. Spin tubes within 2 hrs of collection. Centrifuge in swing-out rotor centrifuge at 1100 RCF for a minimum of 10 min. Freeze plasma aliquot at -20°C. **EDTA tubes** – Store at room temperature for overnight or same day delivery.	☐ **Ambient 15-30°C** – SST tube and EDTA tubes must be shipped ambient within 24 hours of collection. ☐ **Refrigerated 2-8°C** – SST tube must be immediately stored and shipped in cold box with ice packs and received at HDRL within 2-7 days of collection. ☐ **Frozen -20°C** – Ship frozen **aliquoted** specimen with dry ice if specimen will be received at HDRL after 24 hours of collection. **RECOMMENDED**: Ship on 6 lbs. dry ice in case of shipment delay.

Vaccine Construct if known:_____

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)

BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR MSO Version: 08/2017

Appendix B8

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Hepatitis B Surface Antigen Test Request Form

Test Requested	Specimen Requirement	Draw Tube	Shipping Conditions (Check one)
☐ **HBsAg Confirmatory**	☐ 3 ml serum (SST Tubes) or ☐ 3 ml plasma (EDTA, Na Heparin, Na Citrate, CPDA and ACD-1 plasma is acceptable.)	**SST Tubes** – Invert 5X and allow to clot for 30 min (no more than 2 hrs) post-collection. Centrifuge 10 minutes at 1000-1300 RCF in a swing bucket centrifuge. **NOTE:** Tubes MUST be allowed to clot for 30 minutes. **PPT Tubes** – Invert 8-10X. Stable at RT up to 6 hrs. Centrifuge in swing-out rotor centrifuge at 1100 RCF for a minimum of 10 min. Freeze plasma aliquot at -20°C.	☐ **Ambient 15-30°C** – SST tube must be received at HDRL within 7 days of collection. ☐ **Refrigerated 2-8°C** – SST tube must be shipped in cold box with ice packs and received at HDRL within 7 days of collection. ☐ **Frozen -20°C** – Ship frozen **aliquoted** plasma with dry ice if specimen will be received at HDRL after 7 days of collection.

Please fill the request form completely to ensure timely specimen processing.

PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

Form # TR HBsAg Version 06/2017

Appendix B9

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Mycoplasma genitalium Test Request Form

Test Requested	Specimen Requirement	Transport Tube	Storage & Shipping Conditions
☐ M. gen	☐ 2 mL Urine (between black fill lines) ☐ 1 swab/collection site ☐ Pharyngeal ☐ Rectal ☐ Endocervical ☐ Vaginal	**Urine specimen transport tube:** Transfer 2 mL of first-catch urine into urine specimen transport tube from 20-30 mL in preservative free urine collection cup (within 24 of collection). Patient should not have urinated for at least 1 hour prior to collection. **Unisex collection swab:** Refer to Hologic website https://www.hologic.com/sites/default/files/2018-01/AW-16968_001_01_0.pdf	**Refrigerated 2-8° C** – Store & ship specimens at 2-8° C. Specimens must be shipped in cold box with ice packs and received at HDRL next day. **Ambient 15-30° C** – Store & ship specimens at 15-30° C. **RECOMMENDED:** Ship at refrigerated temperature in case of shipment delay.

Please fill the request form completely to ensure timely specimen processing.

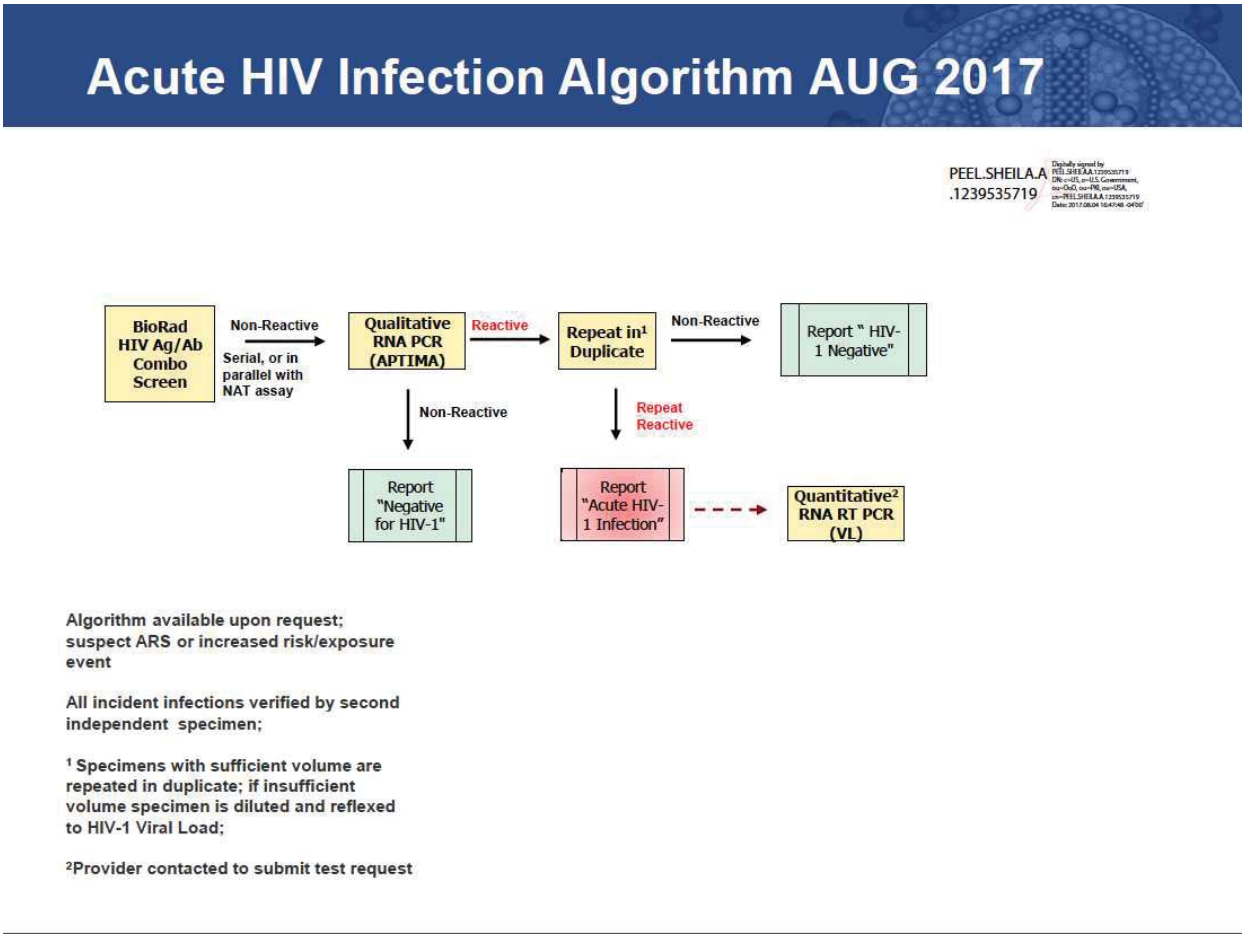
PATIENT IDENTIFICATION	CONTACT INFORMATION
Patient identifiers MUST INCLUDE: **Study #** _____ (If Applicable) **Full Name** _____ **DoD#** _____ **FMP/SSN** _____ **DOB** _____ **Specimen Draw Date / Time:** _____ Ship Date: _____	**POC** _____ **Physician Name** _____ **Clinic / Center** _____ **Center Address** _____ _____ _____ Telephone Number _____ Fax Number _____ (Commercial # only; please include area/country code) Alternate POC Name _____ Alternate POC Phone _____

PROCESSING LAB (For HDRL use only)		
BARCODE	DATE RECEIVED	QUANTITY & TYPE RECEIVED / INITIALS

Fax/Email a FedEx tracking and/or invoice number to ensure all shipments sent to the HIV Diagnostics and Reference Laboratory are received, IAW CAP GEN.40530

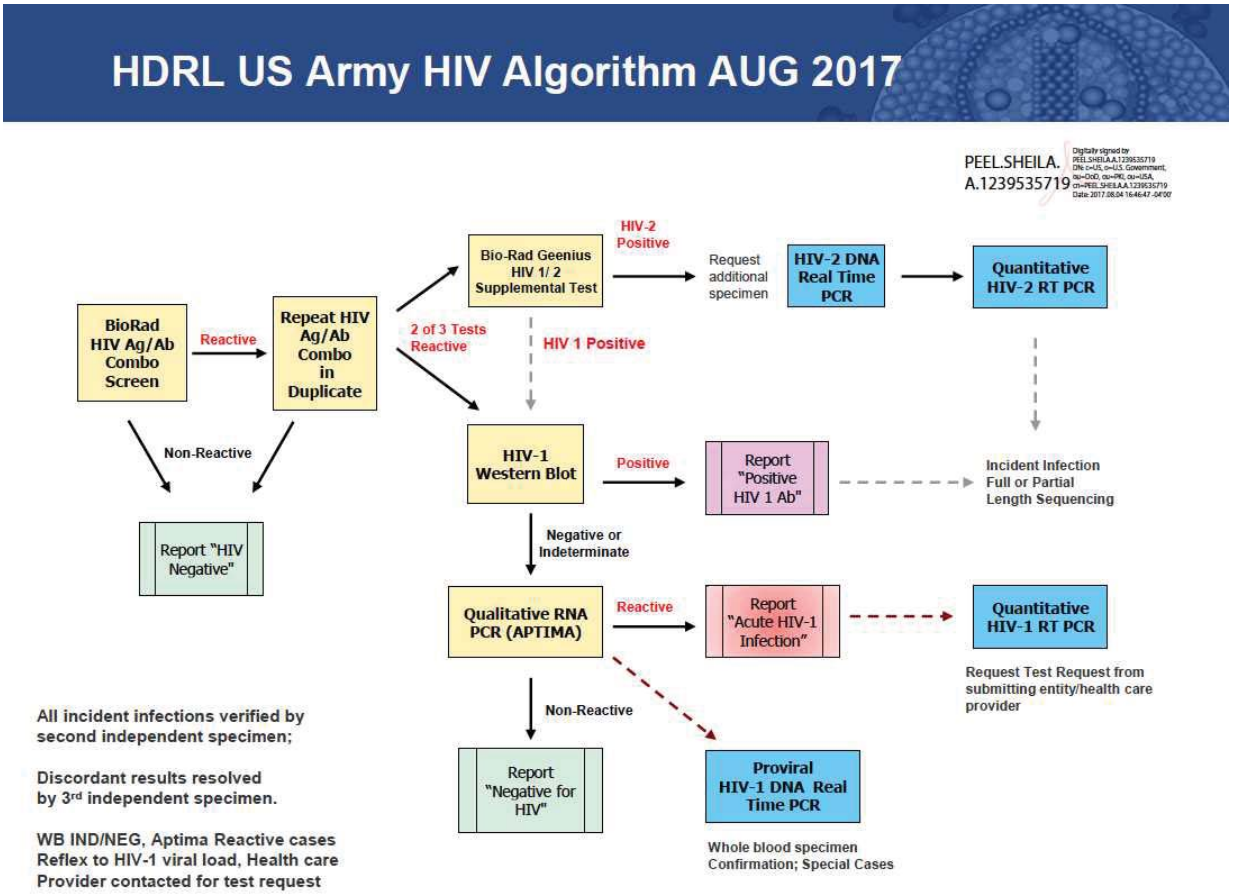
Form # TR MGEN Version: 05/2018

Appendix C: HIV Acute Infection Algorithm



SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix D: HIV Testing Algorithm



SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix E: Packing Instructions

SPECIMEN SUBMISSION GUIDELINES
Department Of Laboratory Diagnostics And Monitoring
Walter Reed Army Institute Of Research
HIV Diagnostics and Reference Laboratory

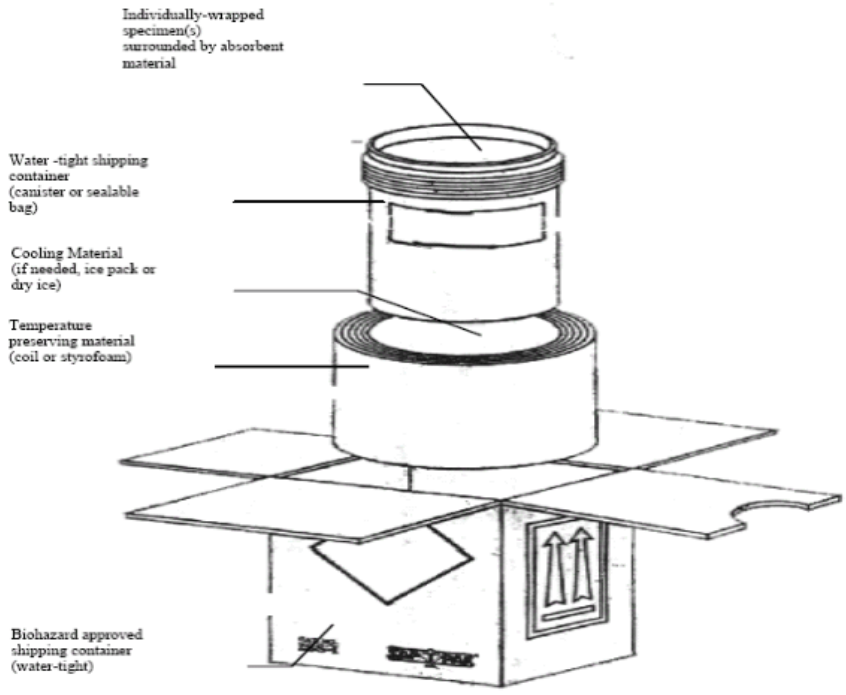
PACKAGING AND SHIPMENT OF SPECIMEN

DO NOT SEND SPECIMENS TO ARRIVE ON WEEKENDS OR FEDERAL HOLIDAYS.

Sites submitting specimens must comply with all applicable Federal and State regulations concerning shipment for diagnostic substances. Minimum requirements for packaging and shipping follow:

A. Package sample in a watertight primary container (ie Sample tube) and secondary container.
B. Surround individually wrapped specimens with enough absorbent material to absorb entire content of tube if spillage occurs during transport.
C. Wrap all vials individually to avoid contact with other tubes.
D. Place each tube in a biohazard bag to contain spillage and avoid contaminating other tubes being shipped in the secondary container.
E. Place request forms within the container in a waterproof sleeve separate from the tubes.
F. Label container and ship specimens according to applicable guidelines (ie 49CFR and IATA regulations) for biological diagnostic shipment of specimens.
G. Mail to: **9100 Brookville Road, BLDG 508, Silver Spring, MD 20910**
H.. **FAX/EMAIL/CALL in A FEDEX TRACKING AND/OR INVOICE NUMBER TO ENSURE ALL SHIPMENTS ARE RECEIVED.**

Note: If you would like your shipping boxes returned to your site, please enclose a prefilled FedEx or address slip with FedEx billing information and material to cover hazardous warnings.



DELETION OR SUBSTITUTION OF ANY REQUIRED COMPONENTS MAY RENDER PACKAGES ILLEGAL FOR SHIPPING INFECTIOUS SUBSTANCES

Shipping Address: 9100 Brookville Road* BLDG. 508 * Silver Spring * MD 20910
Tel: 301-319-3123* Fax: 301-319-3502

Appendix F: Point of Contact Forms

Appendix F1

POINT OF CONTACT FORM – RESULT REPORTING

To maintain the integrity of our database and services, the HIV Diagnostics and Reference Laboratory (HDRL) requests new or updated information from your site. Please review and enter any corrections.

This information pertains to the delivery of **(please check ALL applicable reports):**

- ☐ Serology (HIV EIA, Geenius HIV1/2, Western Blot)
- ☐ Qualitative HIV-1 RNA (Aptima)
- ☐ Qualitative HCV RNA (Aptima)
- ☐ HIV Viral Load
- ☐ HCV Viral Load
- ☐ HIV-1 Resistance Genotyping
- ☐ HIV-1 Integrase Genotyping
- ☐ Viral Phenosense
- ☐ Viral Trofile
- ☐ *Mycoplasma genitalium*
- ☐ Other _____

All Fields are required for Primary POC. Please provide information for Secondary POC if applicable.

Primary POC:	Secondary POC:
_____	_____
Phone Number:	Phone Number:
_____	_____
(Commercial Only)	(Commercial Only)
Fax Number:	Fax Number:
_____	_____
Is this fax secure (in a private office)?	Is this fax secure (in a private office)?
☐ Yes ☐ No	☐ Yes ☐ No
Email Address:	Email Address:
_____	_____

Mailing Address: _____

(Including organization name) _____

Both

_____

Send Results By:

☐ Fax ☐ Fed Ex ☐ Secure File Transfer

Reason for POC change (if applicable):

_____

(e.g., new account, POC moved, different testing, yearly update)

Appendix F2

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

POINT OF CONTACT FORM – NOTIFICATION AND FOLLOW-UP

In order to ensure proper follow-up on reported HIV positive test results, we need information from your site. The Primary POC should be the Provider responsible for discussing the result with the patient. This is to ensure compliance with CAP regulations for report of HIV test results.

Primary POC: _____	**Secondary POC:** _____
Phone Number: _____	**Phone Number:** _____
(Commercial Only)	(Commercial Only)
Fax Number: _____	**Fax Number:** _____
Is this fax secure (in a private office)?	Is this fax secure (in a private office)?
Yes No	Yes No
Email Address: _____	**Email Address:** _____
Mailing Address: _____	**Mailing Address:** _____
_____	_____
_____	_____

Printed name and position title: _____ (Printed name) _____ (Title)

Signature authorizing designation of POCs: _____ (Signature) _____ (Date)

HDRL requires at least two (2) POCs, full addresses, and telephone and fax numbers.

Due to the sensitive nature of HDRL's reports, the POCs will be the only persons HDRL will consult for follow-up information. HDRL may also contact the POCs if questions arise concerning specimens.

Result reports will continue to go through the current mechanisms, but NLT 10 working days post reporting a positive result, HDRL will conduct a follow-up with the primary POC to ensure notification.

Please fax this information to (301) 319 3502. Additionally, keep this form on file and update HDRL with any changes regarding the POCs, addresses, or phone numbers.

For questions, please contact the HDRL Laboratory Manager @ 301-319-3173 or 301-319-3177.

Form# POC NF Version 06/2017

SPECIMEN SUBMISSION GUIDELINES
HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix G1: Verification Kit Instructions

Department of Laboratory Diagnostics and Monitoring
Specimen Processing Laboratory/BioRepository
13 Taft Ct., Room 16, Rockville, MD 20850
Phone (301) 251-8345/ Fax (301) 251-5081

Kit Instructions

You are receiving this package because a patient at your site had a first time positive test result for HIV. This shipment contains everything you need to draw the blood for an HIV verification test and to ship to the Specimen Processing Laboratory/BioRepository (SPL/BioR) within the Department of Laboratory Diagnostics and Monitoring.

PLEASE FOLLOW ALL INSTRUCTIONS CAREFULLY

Blood should ONLY be drawn MONDAY THROUGH THURSDAY.
DO NOT schedule any draws or send kits out Friday, Saturday, or Sunday.

Use kit BEFORE (mm/dd/yyyy)_____D O NOT use expired tubes.
Samples should be processed and shipped on the same day of the blood draw.

1. **This Kit Includes:**
   a. Two (2) CPT Tubes (blue and black tops)
   b. Four (4) PPT Tubes (white top) for a minimum of 4 mL of plasma
   c. Three (3) Cold Packs
   d. One (1) absorbent sheet STP-711
   e. One (1) kPa Bag
   f. One (1) foam block
   g. One (1) UN3373 Biological Substance label
   h. Return FedEx airbill
   i. Test Request Form
   j. Packing Instructions
   k. Example of a completed Test Request Form
2. **Procedure:**
   a. Label tubes with Patient NAME, SSN, DOB. Un-labeled or mislabeled tubes won't be processed.
   b. Complete Test Request Form, ALL fields need to be completed.
   c. Draw tubes to maximum fill point. Invert 8-10 times to mix.
   d. Tube Processing:

	Centrifugation	Shipment
CPT	Spin tubes within 2 hours of collection. Centrifuge in swing-out rotor centrifuge at 1500-1800 RCF for a minimum of 20 min.	Tubes must be immediately shipped in cold box with ice packs and received at the SPL/BioR within 24 hours. **PLEASE EMAIL FEDEX TRACKING NUMBER TO splab@hivresearch.org and Anais Valencia-Ruiz (Laboratory Manager) avalencia-ruiz@hivresearch.org**
PPT	Spin tubes within 4 hours of collection. Centrifuge in swing-out rotor centrifuge at 1100 RCF for a minimum of 10 min.	

   e. Prep original shipment box by following the included Packing Instructions.
   f. Fill in the fields of the Packing Instructions form.
   g. Affix the UN3373 Biological Substance Label to the outside of the box.
   h. Affix the supplied Return FedEx airbill to the box, and schedule a pick up with FedEx.

For questions about the blood draw, or shipment information, please contact **Nia Moses (Study Coordinator) nmoses@hivresearch.org and Anais Valencia-Ruiz (Laboratory Manager) avalencia-ruiz@hivresearch.org.**

Form # KIT INS Version 09/2018

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Appendix G2: Verification Kit Packing Instructions

SPECIMEN SUBMISSION GUIDELINES

HIV Diagnostics and Reference Laboratory
US Military HIV Research Program, Walter Reed Army Institute of Research
9100 Brookville Road, BLDG 508, Silver Spring, MD 20910

Department of Laboratory Diagnostics and Monitoring
Specimen Processing Laboratory/BioRepository
13 Taft Ct., Suite 100, Rockville, MD 20850
Phone: (301) 251-8345/ Fax: (301) 251-5081

PACKING INSTRUCTIONS

IMPORTANT

- **Upon receipt** place Cold Packs in refrigerator (4°C)
- Once kit is packed up, call FedEx to schedule pick up.

Pack Date:_____

Time Samples Added and Box Sealed:

_____AM/PM

Initials of Packer: _____

1. Place One (1) Chilled Cold Pack in bottom of Styrofoam lined kit.

2. Place One (1) Chilled Cold pack against two opposite side walls of the Styrofoam lined kit.

3. Place grey foam containing specimen Tubes into kPa Bag with absorbent sheets and seal bag. (Remove as much air as possible).

4. Place Sealed bag with tubes (with tubes up) between the 4 frozen side bricks on top of the bottom brick.

5. Replace lid. Ensure the filled in Test Request Form and Packing Instructions are placed on top of the lid. Seal box for shipping.

Form # PK INS

Version 09/2018

EXHIBIT C

TRADOC Pamphlet 525-3-1

The U.S. Army in Multi-Domain Operations 2028

6 December 2018

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Foreword

From the Chief of Staff of the Army

America's adversaries have studied US operations closely during Operations DESERT STORM, IRAQI FREEDOM, and ENDURING FREEDOM. They know the American way of war well and that we excel in a way of war that emphasizes joint and combined operations; technological dominance; global power projection; strategic, operational, and tactical maneuver; effective joint fires; sustainment at scale; and mission command initiative.

Simultaneously, emerging technologies like artificial intelligence, hypersonics, machine learning, nanotechnology, and robotics are driving a fundamental change in the character of war. As these technologies mature and their military applications become more clear, the impacts have the potential to revolutionize battlefields unlike anything since the integration of machine guns, tanks, and aviation which began the era of combined arms warfare.

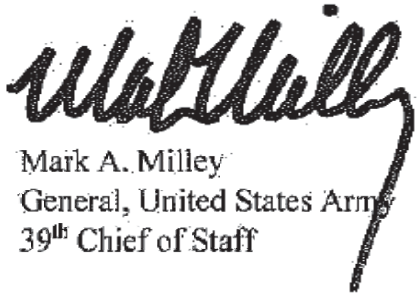
Strategic competitors like Russia and China are synthesizing emerging technologies with their analysis of military doctrine and operations. They are deploying capabilities to fight the US through multiple layers of stand-off in all domains – space, cyber, air, sea, and land. The military problem we face is defeating multiple layers of stand-off in all domains in order to maintain the coherence of our operations.

Therefore, the American way of war must evolve and adapt. *The U.S. Army in Multi-Domain Operations, 2028* is the first step in our doctrinal evolution. It describes how US Army forces, as part of the Joint Force, will militarily compete, penetrate, dis-integrate, and exploit our adversaries in the future.

This product is not a final destination, but is intended to provide a foundation for continued discussion, analysis, and development. We must examine all aspects of our warfighting methods and understand how we enable the joint force on the future battlefield. We must challenge our underlying assumptions, and we must understand the capabilities and goals of our potential enemies. That is how we change our warfighting techniques and build the fighting forces we need in the future. It is also how we maximize deterrence and, if necessary, win future wars.

Read, study, and dissect the multi-domain operations concept in this document. Every one of you is part of our evolution and the construction of the future force, and we want your critical feedback. Our intent is to publish another iteration in about 12 months following feedback from various wargames and exercises. We are laying the cornerstone for the success of our future Army in a profession where there is no room for second place. With your help, we will ensure America's Army is ready, lethal, and prepared to destroy its enemies now and in the future, in any domain, anytime, anywhere.

Army Strong!



Mark A. Milley
General, United States Army
39th Chief of Staff

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Preface

From the Commanding General, U.S. Army Training and Doctrine Command

One of our duties as Army professionals is to think deeply and clearly about the problem of armed conflict in the future so that we can build and prepare our Army to deter that conflict and, if necessary, fight and win it. As we consider the future, our Army's challenge is clear. In a new era of great power competition, our nation's adversaries seek to achieve their strategic aims, short of conflict, by the use of ***layered stand-off*** in the political, military and economic realms to separate the U.S. from our partners. Should conflict come, they will employ ***multiple layers of stand-off*** in ***all domains--land, sea, air, space and cyberspace--***to separate U.S. forces and our allies in time, space, and function in order to defeat us.

If they are successful, we risk losing the strategic depth that gives our Joint Force its operational advantage and enables our offensive military capability. As a nation, we rely on our ability to project power from the Continental United States and to integrate the actions of the Joint Force globally. Our adversaries seek to fracture this capability and erode the United States' strategic advantage--the greatest challenge to U.S. security, power and influence to emerge in the 21st century. The American way of war must evolve if we are to successfully thwart the aims of our adversaries in competition or to defeat them in conflict.

The U.S. Army in Multi-Domain Operations 2028 concept proposes a series of solutions to solve the problem of ***layered standoff***. The **central idea** in solving this problem is the ***rapid and continuous integration of all domains of warfare*** to deter and prevail as we ***compete*** short of armed conflict. If deterrence fails, Army formations, operating as part of the Joint Force, ***penetrate*** and ***dis-integrate*** enemy anti-access and area denial systems; ***exploit*** the resulting freedom of maneuver to defeat enemy systems, formations and objectives and to achieve our own strategic objectives; and consolidate gains to force a ***return to competition*** on terms more favorable to the U.S., our allies and partners.

To achieve this, the Army must evolve our force, and our operations, around three core tenets. ***Calibrated force posture*** combines position and the ability to maneuver across strategic distances. ***Multi-domain formations*** possess the capacity, endurance and capability to access and employ capabilities across all domains to pose multiple and compounding dilemmas on the adversary. ***Convergence*** achieves the rapid and continuous integration of all domains across time, space and capabilities to overmatch the enemy. Underpinning these tenets are mission command and disciplined initiative at all warfighting echelons.

To win tomorrow, we must evolve how we organize and integrate the Army as part of the Joint Force. To do this we will (1) continue to refine a warfighting concept that provides our azimuth to the future--***The U.S. Army in Multi-Domain Operations 2028*** is that concept; (2) develop a comprehensive Army modernization strategy linked to this concept and synchronized with a joint approach to force development; (3) drive rapid, non-linear solutions in Army doctrine, organization, training, material, leadership and education, personnel, facilities, and policy; (4) deepen the operational integration of general purpose and special operations forces and with our allies and partners.

This concept is about warfighting and its centerpiece is the American Soldier. Throughout the United States Army's 243-year history, the grit, ingenuity and initiative of the American Soldier stands at the forefront of our Nation's success in peace, competition, and armed conflict.

As a concept, this is not the final answer. We will refine and update this concept as we learn from our operations, exercises and experiments as well as from other services, allies and partners and even our adversaries. The evolution of this concept into doctrine and practice will inform the way the Army recruits, trains, educates, operates and drives constant improvement and change to ensure the U.S. Army can deter, fight and win on any battlefield, against any foe, now and into the future.

VICTORY STARTS HERE!

Stephen J. Townsend
General, U.S. Army
Commander, TRADOC

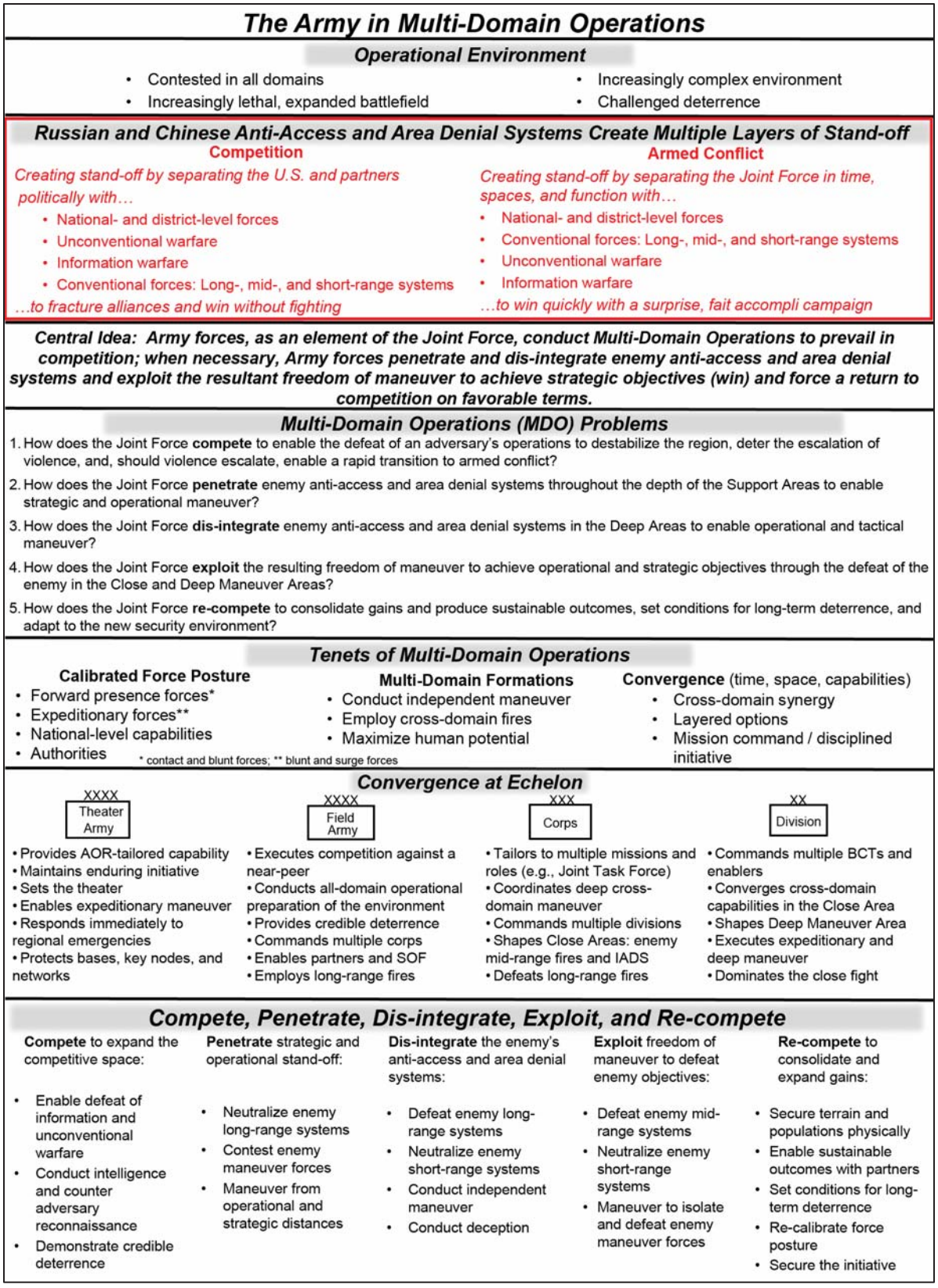

Figure 1. Logic map

Executive Summary

1. **Purpose: From *Multi-Domain Battle* to *Multi-Domain Operations*.** TRADOC Pamphlet 525-3-1, *The U.S. Army in Multi-Domain Operations 2028* expands upon the ideas previously explained in *Multi-Domain Battle: Evolution of Combined Arms for the 21st Century*. It describes how the Army contributes to the Joint Force's principal task as defined in the unclassified *Summary of the National Defense Strategy*: deter and defeat Chinese and Russian aggression in both competition and conflict. *The U.S. Army in Multi-Domain Operations* concept proposes detailed solutions to the specific problems posed by the militaries of post-industrial, information-based states like China and Russia. Although this concept focuses on China and Russia, the ideas also apply to other threats.

2. **The problem.**

a. **Emerging operational environment.** Four interrelated trends are shaping competition and conflict: adversaries are contesting all domains, the electromagnetic spectrum (EMS), and the information environment and U.S. dominance is not assured; smaller armies fight on an expanded battlefield that is increasingly lethal and hyperactive; nation-states have more difficulty in imposing their will within a politically, culturally, technologically, and strategically complex environment; and near-peer states more readily compete below armed conflict making deterrence more challenging.[1] Dramatically increasing rates of urbanization and the strategic importance of cities also ensure that operations will take place within dense urban terrain. Adversaries, such as China and Russia, have leveraged these trends to expand the battlefield in time (a blurred distinction between peace and war), in domains (space and cyberspace), and in geography (now extended into the Strategic Support Area, including the homeland) to create tactical, operational, and strategic stand-off.[2] For the purpose of this document, Russia serves as the pacing threat. In fact, Russia and China are different armies with distinct capabilities, but assessed to operate in a sufficiently similar manner to orient on their capabilities collectively.

b. **China and Russia in competition.** In a state of continuous competition, China and Russia exploit the conditions of the operational environment to achieve their objectives without resorting to armed conflict by fracturing the U.S.'s alliances, partnerships, and resolve. They attempt to create stand-off through the integration of diplomatic and economic actions, unconventional and information warfare (social media, false narratives, cyber attacks), and the actual or threatened employment of conventional forces.[3] By creating instability within countries and alliances, China and Russia create political separation that results in strategic ambiguity reducing the speed of friendly recognition, decision, and reaction. Through these competitive actions, China and Russia believe they can achieve objectives below the threshold of armed conflict.

---

[1] *Hyperactive* means more active than usual or desirable; hyper-competitive during competition and hyper-violent in armed conflict.
[2] Stand-off is the strategic and operational effect Russia, China, and their surrogates are attempting to achieve. It is achieved with both political and military capabilities. Stand-off is the political, temporal, spatial, and functional separation that enables freedom of action in any, some, or all domains, the EMS, and the information environment to achieve strategic and/or operational objectives before an adversary can adequately respond.
[3] Within this document, the term *information warfare* denotes actions taken by an adversary or enemy. The scope and meaning of the term are derived from Russian doctrine. The document refers to friendly actions as *information environment operations.*

c. **China and Russia in armed conflict.** In armed conflict, China and Russia seek to achieve physical stand-off by employing layers of anti-access and area denial systems designed to rapidly inflict unacceptable losses on U.S. and partner military forces and achieve campaign objectives within days, faster than the U.S. can effectively respond. Over the last twenty-five years, China and Russia invested in and developed a systematic approach to "fracture" AirLand Battle by countering the Joint Force's increasingly predictable use of time-phased and domain-federated operational approaches in armed conflict. The resulting anti-access and area denial systems create strategic and operational stand-off that separates the elements of the Joint Force in time, space, and function. Moreover, both China and Russia are continuing to improve these anti-access and area denial systems and are proliferating the associated technologies and techniques to other states. The Joint Force has not kept pace with these developments. It is still designed for operations in relatively uncontested environments that allow for sequential campaigns based on predictable approaches that assume air and naval supremacy: extensive shaping with air and naval strikes before the final destruction of severely degraded enemy forces through joint combined arms operations.

3. **Conducting Multi-Domain Operations.**

a. **Central idea.** Army forces, as an element of the Joint Force, conduct Multi-Domain Operations to prevail in competition; when necessary, Army forces penetrate and dis-integrate enemy anti-access and area denial systems and exploit the resultant freedom of maneuver to achieve strategic objectives (win) and force a return to competition on favorable terms.[4]

b. **Tenets of the Multi-Domain Operations.** The Army solves the problems presented by Chinese and Russian operations in competition and conflict by applying three interrelated tenets: calibrated force posture, multi-domain formations, and convergence. Calibrated force posture is the combination of position and the ability to maneuver across strategic distances. Multi-domain formations possess the capacity, capability, and endurance necessary to operate across multiple domains in contested spaces against a near-peer adversary. Convergence is rapid and continuous integration of capabilities in all domains, the EMS, and information environment that optimizes effects to overmatch the enemy through cross-domain synergy and multiple forms of attack all enabled by mission command and disciplined initiative. The three tenets of the solution are mutually reinforcing and common to all Multi-Domain Operations, though how they are realized will vary by echelon and depend upon the specific operational situation.

c. **Multi-Domain Operations and strategic objectives.** The Joint Force must defeat adversaries and achieve strategic objectives in competition, armed conflict, and in a return to competition. In competition, the Joint Force expands the competitive space through active engagement to counter coercion, unconventional warfare, and information warfare directed against partners.[5] These actions simultaneously deter escalation, defeat attempts by adversaries to "win without fighting," and set conditions for a rapid transition to armed conflict. In armed

[4] *Dis-integrate* refers to breaking the coherence of the enemy's system by destroying or disrupting its subcomponents (such as command and control means, intelligence collection, critical nodes, etc.) degrading its ability to conduct operations while leading to a rapid collapse of the enemy's capabilities or will to fight. This definition revises the current doctrinal defeat mechanism *disintegrate*.
[5] Expanding the competitive space is a key idea from the 2018 *National Defense Strategy*, and is a logical extension of the 2017 *Joint Concept for Integrated Campaigning*. Expanding the competitive space refers to taking actions to expand options (diplomatic, information, military, economic, etc.) for the political leadership and extending competition in time while also deterring escalation to armed conflict.

conflict, the Joint Force defeats aggression by optimizing effects from across multiple domains at decisive spaces to penetrate the enemy's strategic and operational anti-access and area denial systems, dis-integrate the components of the enemy's military system, and exploit freedom of maneuver necessary to achieve strategic and operational objectives that create conditions favorable to a political outcome. In the return to competition, the Joint Force consolidates gains and deters further conflict to allow the regeneration of forces and the re-establishment of a regional security order aligned with U.S. strategic objectives.

d. **Multi-domain problems and solutions.** To achieve these strategic objectives, the Army, as part of and with the Joint Force and partners, must solve five operational problems:

(1) **How does the Joint Force compete to enable the defeat of an adversary's operations to destabilize the region, deter the escalation of violence, and, should violence escalate, enable a rapid transition to armed conflict?** In the past, the U.S. military, due to cultural, statutory, and policy reasons, has often remained reactive in competition below armed conflict. Successful competition requires Army forces actively engaging across domains (including space and cyberspace), in the EMS, and in the information environment. Army forces enable the Joint Force and interagency to seize and sustain the initiative in competition by deterring conflict on terms favorable to the U.S., defeating an adversary's efforts to expand the competitive space below the threshold of conflict, and setting the conditions to enable the Joint Force's rapid transition to armed conflict. The Army's posture, capabilities (to include necessary authorities), and readiness to execute Multi-Domain Operations deter adversaries from escalation, counter their information and unconventional warfare, undermine their efforts to coerce U.S. partners with the threat of armed conflict, and set conditions in the event of conflict. Denying or restricting the support provided by the adversary's conventional forces to proxies allows U.S. partners to more easily counter attempts to destabilize their countries. The demonstrated capability to prevail in armed conflict counters narratives by adversaries who portray the U.S. as a weak or irresolute partner. These actions combine to create a favorable environment for the Joint Force's rapid transition to armed conflict.

(2) **How does the Joint Force penetrate enemy anti-access and area denial systems throughout the depth of the Support Areas to enable strategic and operational maneuver?** In the event of armed conflict, Army forces immediately penetrate enemy anti-access and area denial systems by neutralizing enemy long-range systems, contesting enemy maneuver forces, and maneuvering from strategic and operational distances. Multi-domain formations converge capabilities with the Joint Force and partners to rapidly strike the enemy's long-range systems. Forward presence forces immediately contest an enemy attack in multiple domains. Forward presence forces also preserve lines of communications by degrading enemy long-range surveillance and reconnaissance and by employing a mixture of deception, dispersion, and protection. The appropriate balance of capabilities across the Total Force provides cohesive, fully capable forward presence forces and expeditionary capabilities able to deploy within strategically relevant time periods.

(3) **How does the Joint Force dis-integrate enemy anti-access and area denial systems in the Deep Areas to enable operational and tactical maneuver?** The Joint Force must dis-integrate the enemy's anti-access and area denial systems to further the defeat of the enemy's

stand-off capabilities, prevent the re-integration of remaining capabilities, and enable freedom of maneuver. Army forces at echelon employ cross-domain fires to defeat the enemy's long-range systems and begin the neutralization of the enemy mid-range systems. Convergence optimizes the employment of capabilities across all domains, the EMS, and the information environment to stimulate, see, and strike the enemy. Convergence also complicates the enemy's attempts to conceal and defend its long- and mid-range systems by providing the Joint Force with multiple options for attacking the enemy's vulnerabilities. Joint, Army, and partner maneuver forces execute operational maneuver and deception to further stimulate enemy mid-range systems and fix or isolate enemy maneuver forces.

(4) **How does the Joint Force exploit the resulting freedom of maneuver to achieve operational and strategic objectives through the defeat of the enemy in the Close and Deep Maneuver Areas?** In the Close and Deep Maneuver Areas, Army forces exploit weaknesses in the enemy's command system and their dependence on air defense and ground fires to complete the defeat of the enemy. Army forces employ deception and convergence with other domains to dislocate the enemy defense by physically, virtually, and cognitively isolating its subordinate elements, allowing friendly forces to achieve overmatch and favorable force ratios. The Joint Force continues dis-integrating tactical anti-access and area denial systems to enable further exploitation until it achieves U.S. campaign objectives.

(5) **How does the Joint Force re-compete to consolidate gains and produce sustainable outcomes, set conditions for long-term deterrence, and adapt to the new security environment?** Army forces consolidate gains and set conditions for a favorable new security environment by maintaining control of key terrain and populations that provide U.S. policymakers with a political advantage. They consolidate gains through three concurrent activities: physically securing terrain and populations for sustainable outcomes; setting conditions for long-term deterrence by regenerating partner and Joint Force capacity and by actively engaging across domains and the information space; and adapting force posture to the new security environment. This provides time for U.S. forces to regenerate regional military structures and continue to provide a credible deterrent.

4. **Implications for the Army.**

a. **Enhanced and broader need for combined arms maneuver.** The emerging operational environment and the challenges posed by China and Russia, particularly their capability to create political and military stand-off, demand that the Joint Force apply the proven principles of combined arms maneuver and massing of effects at decisive spaces. What is different is the idea that Army forces must apply these joint capabilities more comprehensively (earlier, in greater capacity, and at lower echelons) and in new ways (faster and with greater agility). Multi-domain formations provide the Joint Force with additional means to stimulate, see, and strike key components and vulnerabilities within enemy systems. Army forces also continue to conduct the traditional tasks of seizing terrain, destroying enemy forces, and securing friendly populations. Army forces retain the ability to overmatch the enemy, despite reduced friendly capacity, by converging capabilities from across all domains, the EMS, and the information environment.

b. **Operating at echelon.** Army forces execute Multi-Domain Operations with echeloned formations that conduct intelligence, maneuver, and strike activities across all five domains (air, land, maritime, space, and cyberspace) as well as the information environment and the EMS.[6] The ability of Army formations at echelon to converge capabilities in multiple ways and sequences provide the Joint Force Commander with options to impose additional complexity on the enemy. The echeloning of forces prevents the isolation of forward positioned forces within the stand-off range of enemy anti-access and area denial systems at the beginning of a conflict and enables strategic and operational maneuver by forces from outside the range of anti-access and area denial systems. Maneuver at echelon by Army forces then enables the Joint Force to overwhelm Chinese and Russian military systems with multiple dilemmas and massed effects, creating windows of superiority to enable freedom of maneuver.[7]

c. **Converging cross-domain capabilities.** Convergence has two advantages over single-domain alternatives: cross-domain synergy creates overmatch and multiple forms of attack create layered options across domains to enhance friendly operations and impose complexity on the enemy. The ability to converge cross-domain capabilities enables the Joint Force to stimulate, see, and strike vulnerabilities in the Chinese and Russian systems and defeat their efforts to create stand-off.[8] Currently, the Joint Force converges capabilities through the episodic synchronization of domain-federated solutions, but will have to conduct continuous and rapid integration of multi-domain capabilities enabled by mission command and disciplined initiative against near-pear threats in the future.

d. **Maximize human potential.** The Army builds and sustains multi-domain formations through the selection, training, and education of the leaders, Soldiers, and teams in them. Employing multi-domain capabilities requires the Army to attract, retain, and employ leaders and Soldiers who collectively possess a significant breadth and depth of technical and professional expertise. The Army must exercise careful talent management to make the most of these high-quality personnel and integrate them into trusted teams of professionals who are able to thrive in ambiguity and chaos. Improving the resilience of leaders and Soldiers—the Army's most valuable capability—requires training, educating, equipping, and supporting them to execute Multi-Domain Operations in all of its intensity, rigor, and complexity.

e. **Required Army capability sets.** *The U.S. Army in Multi-Domain Operations* concept requires the Army to develop or improve capabilities to contribute cross-domain options within the Joint Force by:

[6] The *U.S. Army Functional Concept for Movement and Maneuver, 2020-2040* defines cross-domain maneuver as "the employment of mutually supporting lethal and nonlethal capabilities in multiple domains to generate overmatch, present multiple dilemmas to the enemy, and enable Joint Force freedom of movement and action."
[7] As an example, Army formations can maneuver—or assist Joint Force maneuver—as a reconnaissance action, fighting to gain intelligence, key terrain, and set conditions that enable strikes, rather than maneuvering only after passive intelligence collection, deliberate analysis, and precision strikes have prepared the battlefield for maneuver.
[8] The *U.S. Army Concept for Multi-Domain Combined Arms at Echelons Above Brigade, 2025-2045* calls for formations able to integrate, synchronize, and converge all elements of combat power across all domains, the EMS, and the information environment to execute cross-domain maneuver; provide essential linkage to the expanded instruments of national power; and operate ubiquitously with joint, interagency, and multinational partners to overmatch any threat in any future environment.

(1) Calibrating force posture geographically and across all the Army components to defeat Chinese and Russian offensive operations in competition and to deter escalation to armed conflict.[9]

(2) Preparing the operational environment by building partner capacity and interoperability and setting the theater through such activities as establishing basing and access rights, prepositioning equipment and supplies, conducting preparatory intelligence activities, and mapping EMS and computer networks.[10] (Supported by Army Materiel Modernization Priorities: Army Network)

(3) Building partners' and allies' capacities and capabilities to defeat increasingly sophisticated Chinese and Russian-sponsored unconventional and information warfare.

(4) Preparing the operational environment for competition and conflict by building understanding of and capabilities in select urban areas of particular operational or strategic importance.

(5) Establishing precision logistics that provides a reliable, agile, and responsive sustainment capability necessary to support rapid power projection, Multi-Domain Operations, and independent maneuver from the Strategic Support Area to the Deep Maneuver Area. (Supported by Army Materiel Modernization Priorities: Future Vertical Lift, Army Network)

(6) Establishing necessary authorities and permissions normally reserved for conflict or to higher echelons to operate in competition and rapidly transition to conflict effectively.

(7) Improving the capability to conduct Multi-Domain Operations in dense urban terrain at all echelons through the development of tactics and capabilities to increase the accuracy, speed, and synchronization of lethal and nonlethal effects. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicle, Army Network, Soldier Lethality)

(8) Supporting a credible U.S. information narrative through cross-domain actions that communicate and counter threats by Chinese and Russian reconnaissance, strike, combined arms, and unconventional warfare capabilities.

(9) Enabling commanders and staffs at each echelon to visualize and command a battle in all domains, the EMS, and the information environment, converging organic and external capabilities at decisive spaces. This requires new tools to more rapidly converge capabilities across the Joint Force, shifting training paradigms, and changing personnel and talent management practices. This also requires that Army formations be trained, manned, and equipped to leverage all available information, from national, joint, commercial, and Service repositories and libraries, or directly from collection assets seamlessly and in a time dominant

[9] The idea of calibrating and re-calibrating force posture globally aligns with the idea of "forming operationally coherent forces" as described in the Joint Concept for Rapid Aggregation.
[10] "Setting the theater" encompasses the actions to establish and maintain conditions to seize the initiative and retain freedom of action for a specific theater. These actions may occur outside of the theater as well.

manner. (Supported by Army Materiel Modernization Priorities: Army Network, Soldier Lethality, Synthetic Training Environment)

(10) Providing to the Joint Force Commander multi-domain formations and systems that can converge capabilities to attack specific vulnerabilities in Chinese and Russian multi-layered, mutually reinforcing military forces and systems. This means creating commanders and staffs who have the means and ability to access and employ capabilities that reside across the Joint Force. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Soldier Lethality)

(11) Providing to the Joint Force Commander with multi-domain formations that have systems, leaders, and Soldiers that are durable, can operate in a highly contested operational environment, cannot easily be isolated from the rest of the Joint Force or from partners, and are able to conduct independent maneuver and employ cross-domain fires. This requires extended sustainability of systems and formations, and leaders and Soldiers who continue to operate effectively in austere environments and conditions. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Army Network, Air and Missile Defense, Soldier Lethality)

(12) Consolidating gains through clear demonstrations of U.S. security commitments to partners through combined exercises, training, information exchanges, and other presence activities.

(13) Enabling and complementing land, air, and maritime capabilities with operations in space, cyberspace, and the EMS to support the opening of and exploitation of windows of superiority that create dilemmas for the enemy while protecting the ability to conduct friendly operations in degraded, disrupted, and/or denied operational environments.

(14) Attracting, retaining, and making maximum use of high-quality, physically fit, mentally tough Soldiers who have the skills and expertise to conduct Multi-Domain Operations.

f. Success in Multi-Domain Operations requires these capabilities be sufficiently developed, trained, and practiced within the Army, with the remainder of the Joint Force, and with allies and partners.

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***TRADOC Pamphlet 525-3-1**

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Military Operations

THE U.S. ARMY IN MULTI-DOMAIN OPERATIONS 2028

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History. This is a major revision of the U.S. Army Training and Doctrine Command (TRADOC) Pamphlet 525-3-1. It replaces *The U.S. Army Operating Concept: Win in a Complex World*, and the *Multi-Domain Battle: Evolution of Combined Arms for the 21st Century* concept.

Summary. This pamphlet describes how Army forces contribute to the Joint Force's principal task as defined in the unclassified *Summary of the National Defense Strategy:* deter and defeat Chinese and Russian aggression in both competition and conflict.

Applicability. This document applies to all Department of the Army (DA) activities that develop doctrine, organization, training, materiel, leadership and education, personnel, and facilities (DOTMLPF) capabilities. It guides future force development and informs the Joint Capabilities Integration and Development System process. It also supports Army capabilities development processes and functions as a conceptual basis for developing supporting concepts related to the future force within DOTMLPF.

Proponent: The proponent of this document is the Director, Concept Development and Learning Directorate, Army Capabilities Integration Center (ATFC-ED), 950 Jefferson Avenue, Fort Eustis, VA 23604-5763.

*This pamphlet supersedes TRADOC Pamphlet 525-3-1, dated 31 October 2014.

Suggested improvements. Users are invited to submit comments and suggested improvements. Comments may be provided via DA Form 2028 to Director, ARCIC (ATFC-ED), 950 Jefferson Avenue, Fort Eustis, Virginia 23604-5763.

Availability. The official published version of this pamphlet is available on the TRADOC Administrative Publications website (http://adminpubs.tradoc.army.mil/). It is also available at the Joint and Army Concept Division DODTechSpace at https://www.dtic.mil/dodtechspace/groups/army-capabilities-integration-center/projects/joint-and-army-concepts-division.

Summary of Change

TRADOC Pamphlet 525-3-1
The U.S. Army in Multi-Domain Operations 2028

This major revision, dated 27 November 2018-

o Describes how Army forces contribute the Joint Force's principal task to deter and defeat Chinese and Russian aggression in both competition and armed conflict as outlined in the unclassified *Summary of the National Defense Strategy.*

o Provides a threat-based approach to operations against near-peer adversaries.

o Addresses operations in competition, armed conflict, and the transition back to competition (return to competition).

o Describes how Army forces fight across all domains, the electromagnetic spectrum, and the information environment and at echelon.

o Introduces or revises the terms: Multi-Domain Operations, calibrated force posture, convergence, multi-domain formations, decisive space, independent maneuver, dense urban terrain, dis-integrate, information space, stand-off, and precision logistics.

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Chapter 1
Introduction

1-1. Purpose
United States (U.S.) Army Training and Doctrine Command (TRADOC) Pamphlet 525-3-1, *The U.S. Army in Multi-Domain Operations* describes how Army forces contribute to the Joint Force's principal task as defined in the unclassified *Summary of the National Defense Strategy:* deter and defeat Chinese and Russian aggression in both competition and conflict.[11] *The U.S. Army in Multi-Domain Operations* proposes detailed solutions to the specific problems posed by the militaries of post-industrial, information-based states like China and Russia. Although this concept focuses on China and Russia, the ideas also apply to other threats. The concept describes the Army in 2028, though some of the capabilities described might not be fully fielded across the entire force by that time.

1-2. Methodology and organization
The *U.S. Army Multi-Domain Operations* concept describes how Army forces fight across all domains, the electromagnetic spectrum (EMS), and the information environment and at echelon. The concept is based on extensive analyses, wargaming, experimentation, and collaboration with other Services and the Joint Staff. Chapter 2 describes the characteristics, capabilities, and vulnerabilities of Chinese and Russian anti-access and area denial systems in competition and in conflict. Chapter 3 describes the military problem, gives a detailed description of the tenets of Multi-Domain Operations (MDO), and then provides detailed descriptions of their application to solve the five multi-domain problems. Chapter 4 summarizes the immediate implications of MDO and describes the path of future concept development.

1-3. Major changes from Multi-Domain Battle

a. Title changed to *The U.S. Army in Multi-Domain Operations* to better reflect the broader scope of competition and conflict and the inherently joint nature of modern warfare.

b. Insights from the U.S. Army Mosul Study and North Atlantic Treaty Organization (NATO) Urbanization Project informed revisions to the description of the emerging operational environment, refinements to the solution, and a new dense urban terrain appendix.

c. Insights gained from wargames, simulations, Joint Warfighting Assessments, and joint and multi-Service collaboration are incorporated into refined descriptions of Chinese and Russian systems, tenets of MDO, and required capabilities.

d. Provides much greater detail regarding the application of MDO as a basis for functional concept development, further experimentation, and force development.

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[11] The *U.S. Army in Multi-Domain Operations, 2028* concept is a single Service concept and therefore refers to "Army forces," even in instances when "ground forces" could also be used because U.S. Marine Corps units would operate differently within their Service structures. Similarly, "Army forces" is also used in instances describing the use of space, cyberspace, electronic warfare, intelligence, surveillance, and reconnaissance capabilities that are possessed by one or more of the other Services, but because the Services organize and operate differently, limits the description to Army forces. This concept reinforces the requirement for multi-Service and joint operations in new ways without prescribing roles, functions, and organization for the other Services or partners. The concept strengthens the idea that the Army will operate as an element of the Joint Force in the execution of Multi-Domain Operations.

Chapter 2
The Operational Context

2-1. The emerging operational environment

a. The *Joint Operating Environment 2035* predicts that for the foreseeable future, U.S. national interests will face challenges from both persistent disorder and states contesting international norms.[12] This concept addresses the second of those challenges. As the Joint Force responds to adversaries contesting international norms in either competition or armed conflict, it will conduct operations in an emerging operational environment shaped by four interrelated characteristics: adversaries are contesting all domains, the EMS, and the information environment and U.S. dominance is not assured; smaller armies fight on an expanded battlefield that is increasingly lethal and hyperactive; nation-states have more difficulty in imposing their will within a politically, culturally, technologically, and strategically complex environment; and near-peer states more readily compete below armed conflict, making deterrence more challenging. These characteristics allow adversaries, particularly near-peer threats like China and Russia, to expand the battlefield in time (a blurred distinction between peace and war), in domains (space and cyberspace), and in geography (now extended into the homeland) to create tactical, operational, and strategic stand-off.

b. An additional important characteristic of the emerging operational environment is its urban nature. The strategic importance of cities suggests that Army forces will have to conduct operations within dense urban terrain.[13] The physical and demographic density of this environment creates distinct physical, cognitive, and operational characteristics. The cumulative effect of these factors compounds the friction of war by increasing the number of tasks required within a given physical or temporal space while multiplying the tactical, operational, and strategic variables that commanders and staffs must take into account. Operations in dense urban terrain might be in response to either persistent disorder or to contested norms. In the latter case, adversaries will exploit dense urban terrain to gain advantage or to mitigate the Joint Force's strengths.[14]

c. Among the states most likely to contest international norms, China and Russia prove the most capable. They are, therefore, the focus of this concept. As described below, both China and Russia are pursuing capabilities and approaches to create the same effect of operational and strategic stand-off, though by somewhat different means. This concept assumes—for the purposes of organizing a strategic and operational construct—that Chinese and Russia concept and force development are sufficiently similar for the Army to solve the problems presented by Russia in the near- to mid-term and adapt to the changes China develops in the mid- to far-term.

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[12] Contested norms involve increasingly powerful revisionist states and select non-state actors using all elements of power to establish their own set of rules unfavorable to the U.S. and its interests. Persistent disorder is characterized by an array of weak states that become increasingly incapable of maintaining domestic order or good governance. Publications supporting this assessment include the *Joint Operating Environment 2035*; Worldwide Threat Assessment of the U.S. Intelligence Community, Senate Select Committee on Intelligence, Feb 2016; Military and Security Developments Involving the People's Republic of China 2015, Annual Report to Congress; and David E. Johnson, *The Challenges of the "Now" and Their Implications for the U.S. Army* (Santa Monica, Calif: RAND Corporation, 2016).

[13] Dense urban terrain is "areas characterized by extraordinarily closely-packed manmade infrastructure and high population density, potentially including concentrations of high-rise buildings, subterranean features, and densely packed slums." There is no formal doctrinal term; both dense urban terrain and dense urban environments are used synonymously. For purposes of this concept, dense urban terrain is used.

[14] Appendix D provides a more comprehensive description of Multi-Domain Operations in dense urban terrain.

This document, therefore, accounts for both China and Russia's approaches to create stand-off, but uses Russia as the present pacing threat for technical and tactical purposes.[15]

(1) Russia has demonstrated the intent and the most effective combinations of systems and concepts to challenge the U.S. and its allies militarily in the near term. Russia's actions in Georgia, Ukraine, and Syria have demonstrated their intent to fracture the relationship between the U.S. and its partners and their ability to pursue strategic objectives below the threshold of armed conflict. Russia uses unconventional and information warfare to propagate a narrative that breeds ambiguity and delays the reactions of their adversaries. Over the last decade, Russia has increased its investments in anti-access and area denial capabilities and systems intended to deny the Joint Force entry into a contested area and set the conditions for a *fait accompli* attack.

(2) China possesses the vision and strategic depth to become the U.S.'s most powerful competitor in time. Unlike Russia, China has the economy and technological base, such as an independent microelectronics industry and world-leading artificial intelligence development process, sufficient to overtake current Russian system overmatch in the next 10-15 years. China is rapidly building a world class military intended to project power globally. In the future, China will become the conceptual pacing threat for the Joint Force. The risk associated with this assumption will be continuously assessed to ensure the ability to adapt conceptually should China accelerate its capability development.

d. Chinese and Russian attempts to create political and military stand-off challenge the Joint Force's ability to dominate all domains, the EMS, and the information environment. If successful, stand-off grants these near-peer competitors the strategic freedom of action to pursue objectives at the expense of the U.S. and its allies.[16] They, in conjunction with aligned state and non-state actors, will increasingly challenge the global order by undermining U.S. security guarantees to allies and partners. Vulnerable fault-line states are the principal targets of Chinese and Russian offensive operations short of armed conflict, which are calculated to avoid triggering a decisive U.S. response. China and Russia's ability to escalate through a rapid transition to overt military action provides them the means to seize and maintain the initiative before U.S. and partner forces can prepare a response.

e. Within this emerging operational environment, China and Russia employ a variety of political and military anti-access and area denial strategies and systems to create stand-off in competition and conflict. In competition, both states seek to fracture U.S. alliances and partnerships through a combination of diplomatic and economic actions; unconventional warfare; information warfare; exploitation of social, ethnic, or nationalistic tensions in a region; and the actual or threatened employment of conventional forces. By generating instability within countries and alliances, they create political separation that results in strategic ambiguity, reducing the speed of friendly recognition, decision, and reaction. In armed conflict, China and Russia employ anti-access and area denial systems to create strategic and operational stand-off to separate elements of the Joint Force in time, space, and function.

[15] Both China and Russia require individual, classified tactical and operational battlefield development plans for solution development, analysis, and requirements determination. These plans are under development; they have and will continue to inform *Multi-Domain Operations*.
[16] The National Defense Strategy describes Russian and China as competitors and states that "Long-term strategic competitions with China and Russia are the principal priorities for the Department [of Defense]," *Unclassified Summary of the National Defense Strategy*, pg. 1, 4

f. The emerging operational environment and the threat necessitate adapting the Joint Force's current understanding of the battlefield. Adversaries have expanded the battlefield in four ways: in time (phases), domains, geography (space and depth), and actors. They have blurred the distinctions between actions "below armed conflict" and "conflict," enabling the achievement of strategic objectives short of what the U.S. traditionally considers "war." They have expanded the battlefield by making space, cyberspace, electronic warfare, and information key components of their operations. Potential adversaries have also expanded the battlefield geographically because the effects of their multi-domain capabilities are less bound by geographic and time constraints and extend the range in which formations are under "contact." Finally, they rely on an increasing number of "non-traditional" actors, including proxies and surrogates, to pursue their objectives.

g. The framework depicted in figure 2-1 illustrates the breadth of activities, spaces, distances, and interrelationships for which MDO must account. This concept uses this framework throughout to illustrate friendly as well as an adversary's actions in and across spaces. Despite the linear depiction in figure 2-1, the areas are not defined by fixed geographic relationships or dimensions but by the operational context, the interplay of friendly and enemy capabilities, and terrain. The areas are not self-contained. Instead, the principal utility of the framework is that it allows commanders and staffs to visualize the relationships between actions that take place across the depth of the expanded battlefield. A more detailed description of the framework is found in appendix C.

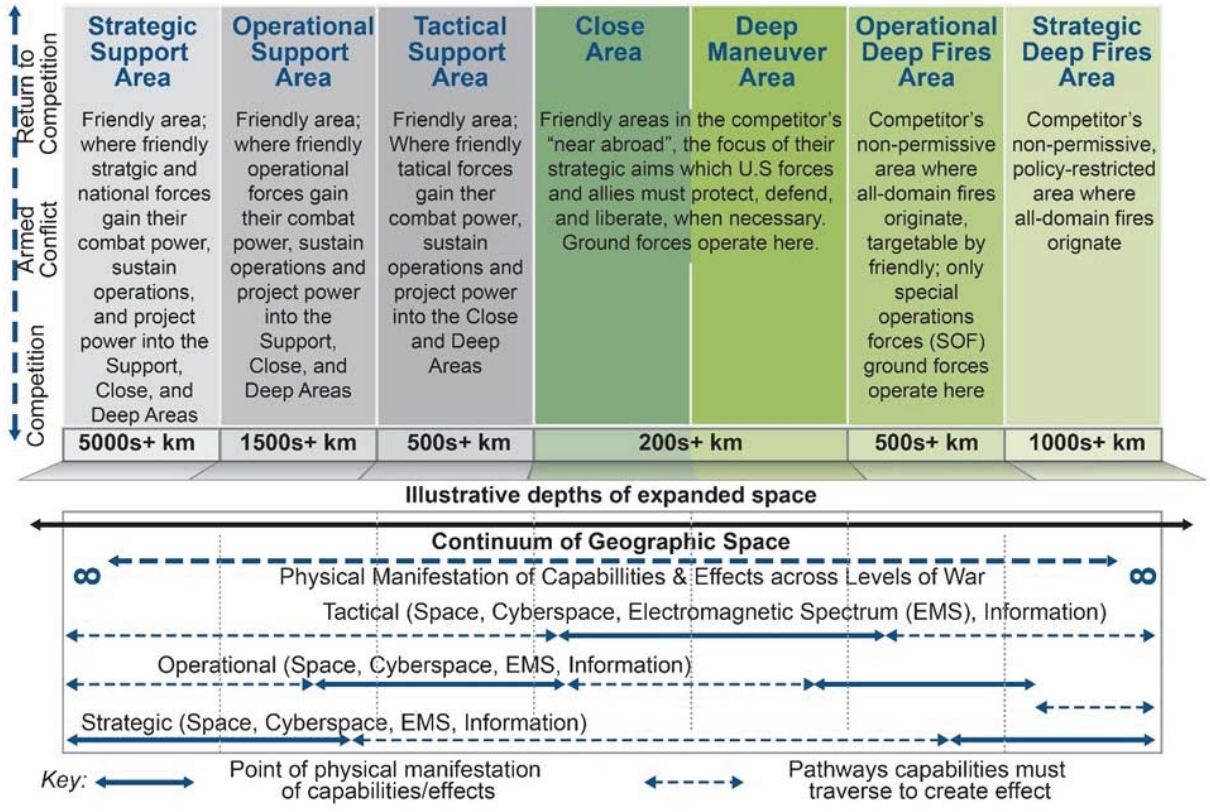

Figure 2-1. MDO framework

2-2. Russia: Achieve objectives in competition below armed conflict[17]

a. In competition, Russia attempts to separate the U.S. and friendly states politically, limiting a coordinated allied response and destabilizing target states. To accomplish this task, Russia executes coordinated campaigns employing national- and district-level capabilities, information warfare (social media, false narratives, cyber attacks), and unconventional warfare to achieve strategic objectives. Russia leverages the presence and posture of conventional forces to both actively support these efforts and demonstrate the capability to rapidly transition to armed conflict (e.g., "snap drills"). This posture also provides Russia with an escalation advantage, because their conventional forces threaten the Joint Force's freedom of action in the air and space and its ability to conduct expeditionary maneuver (see figure 2-2).[18] Through these competitive actions, Russia seeks to achieve objectives without risking armed conflict with the U.S.

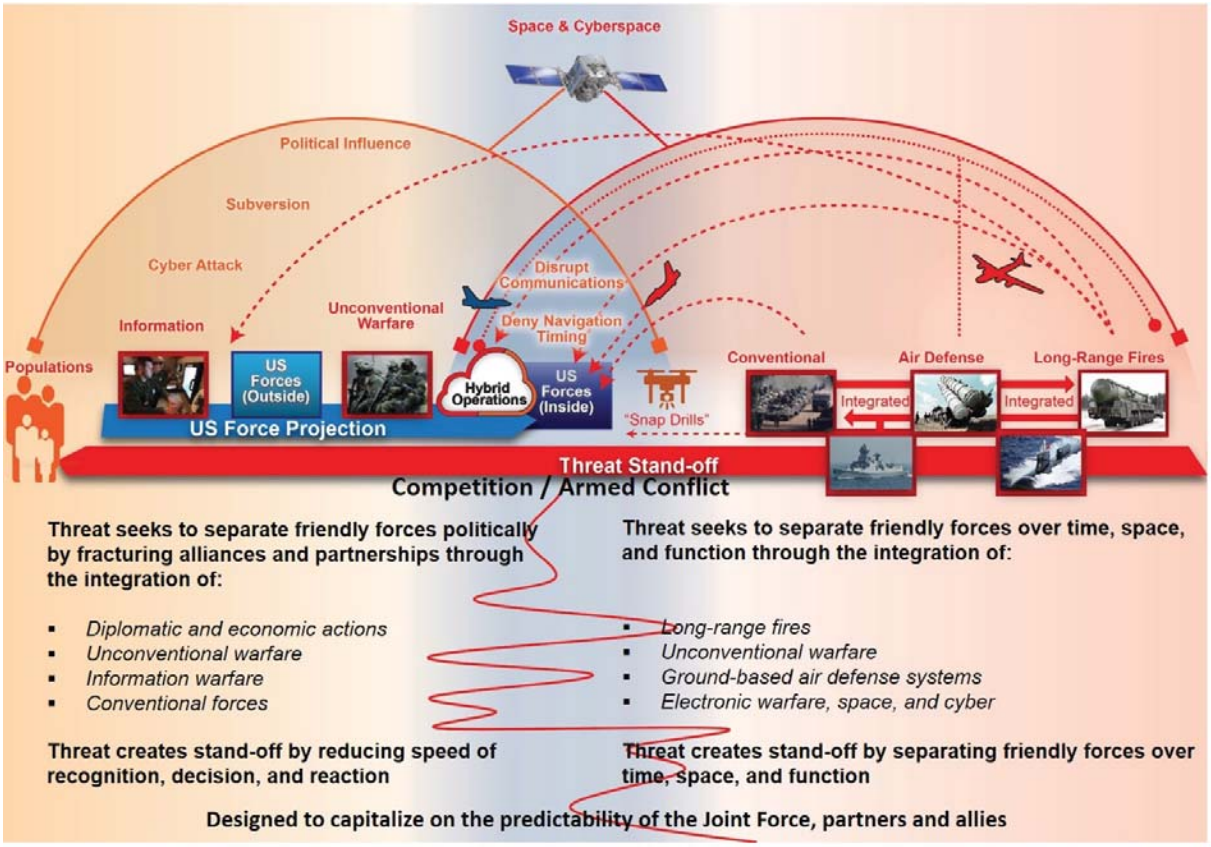

Figure 2-2. China and Russia in competition and armed conflict

b. **National- and district-level capabilities**. Russian national- and district-level capabilities hold the U.S. homeland at risk and threaten expeditionary maneuver.

[17] Sections 2-2, 2-3, and 2-4 describe how Russian forces (the pacing threat) operate. It is assumed that China and other Chinese and Russian proxies operate with characteristics sufficiently similar to use Russian operations as a basis for analysis.
[18] An escalation advantage is essentially a dynamic position of relative advantage, generally achieved by conventional forces.

(1) Russian national-level intelligence, surveillance, and reconnaissance (ISR) assets collect targeting information on fixed sites (headquarters, communications, critical infrastructure, and power projection facilities), detect predictable friendly patterns of operations, and monitor changes to friendly force posture. Space-based reconnaissance, special operations forces (SOF) and sympathizers, open-source collection, ground-based signal intercept platforms, and the communications network linking these sensors to headquarters are the most important ISR capabilities retained at the national and military district levels. Nuclear and other weapons of mass effect (to include widespread cyberspace attacks) threaten the U.S. homeland, allies and partners, and friendly military forces.

(2) Russia conducts active, persistent surveillance of adjoining states, regional allies, and the U.S. homeland. They focus on U.S. capabilities that enable a rapid response, such as Joint Force intelligence collection and transmission, air superiority control and sustainment, and power projection facilities. Russian surveillance enables long-range strikes with ballistic missiles, cruise missiles, offensive cyber, and SOF direct action teams. These strike capabilities support their information narrative in competition by assisting them in controlling escalation on their terms. National- and district-level ISR capabilities enable Russia to determine whether they have achieved the necessary correlation of forces to continue offensive operations in competition. Comprehensive ISR by national- and district-level assets in competition also enables their conventional forces to transition rapidly to armed conflict.

c. **Unconventional warfare.** Russian SOF, local paramilitaries, and activists conduct unconventional warfare to destabilize targeted governments by separating their control of certain regions or populations. Russian unconventional warfare activities empower proxies and activist networks to conduct a range of operations, including terrorism, subversion, destabilizing criminal activities, reconnaissance, information warfare, and direct action strikes. These actions add physical support to their information narrative. Unconventional warfare capabilities support conventional forces with reconnaissance and the ability to exert influence or control over some elements of terrain and populations within U.S. partner territory.

d. **Information warfare.**[19] Russian information warfare is composed of the information narrative and information warfare capabilities. Information warfare works with, and is supported by, their national-level capabilities and unconventional and conventional warfare activities.[20] Adversaries seek to influence both domestic and foreign audiences.[21] Information warfare often involves cyber reconnaissance and strike actions that support other reconnaissance, unconventional, and conventional warfare activities. Information warfare can be destructive, using offensive cyber capabilities to disable, monitor, or spoof friendly and civilian command networks. An increasingly prevalent form of information warfare is the "firehose of falsehood"—fabricated stories distributed by paid "trolls" or automated "bots" that unsuspecting citizens amplify through social media or other means—to confuse audiences or divert attention

[19] This concept refers to an adversary's actions by the Russian doctrinal term *information warfare* and friendly actions by the term *information environment operations*. For Russia, information warfare embodies their plans for information confrontation that includes targeting all aspects of a society—diplomatic, economic, military, political, cultural, social, and religious information arenas. (http://freebeacon.com/national-security/dia-reveals-new-details-russian-information-warfare/)
[20] Russian information warfare capabilities are largely cyber.
[21] An information warfare (or information environment operation for friendly usage) campaign employs various information related capabilities working together toward a common strategic or operational objective.

from adversaries' intentions.[22] This form of information warfare creates ambiguity to prevent or delay political recognition, decision, and reaction.

e. **Conventional forces.** Russia postures conventional forces in competition to create a favorable correlation of forces in regard to the Joint Force and its partners. Exercises, demonstrations, and "snap drills" generate force readiness and stimulate friendly response patterns for their national- and district-level ISR capabilities to collect and analyze. Russian conventional forces possess the demonstrated ability to conduct a *fait accompli* attack with limited warning.[23] Russian surface-to-surface missiles, long-range surface-to-air missiles (SAM), counterspace, and combined arms ground forces are in position to physically isolate U.S. partners and destroy forward-positioned defenders before the Joint Force can respond effectively. This local military superiority supports information narratives of Russian strength and postures their conventional forces to support unconventional warfare directly through covert assistance or indirectly by providing them with an escalation advantage that constrains friendly responses.

f. **Summary of Russian systems in competition.** The operational center of gravity for Russian actions in competition is the close integration of information warfare, unconventional warfare, and conventional forces. The ability to employ all elements in a coordinated manner provides Russia with an escalation advantage, in which any friendly reaction risks a more powerful response. Within competition, the most extreme escalation is the transition to armed conflict, which favors an adversary with the ability to conduct a *fait accompli* attack with their conventional forces. The demonstrated ability to accomplish a *fait accompli* provides credibility to Russian information narratives. The combination of information warfare, unconventional warfare, and conventional and nuclear forces provides Russia with political and military stand-off within which they can secure strategic objectives short of armed conflict with the U.S. Information warfare and unconventional warfare contribute to the destabilization of regional security, but are insufficient in themselves to achieve all Russian strategic objectives. The escalation advantage provided by conventional forces supplements information warfare and unconventional warfare, enabling Russia to maintain the initiative in competition.

2-3. Russia in armed conflict: Separate the Joint Force and create strategic and operational stand-off

a. Russian conventional forces seek to further enhance physical stand-off by creating layers of anti-access and area denial systems designed to inflict unacceptable losses on U.S. and partner military forces and to achieve campaign objectives within days, before the U.S. can effectively respond. These forces are enabled by all-domain reconnaissance that operates in depth, from as deep as the U.S. homeland to the area of operations. Empowered by extensive reconnaissance complexes, these threats can conduct simultaneous attacks throughout the depth of the battlefield. Russian systems are designed to separate the Joint Force in time, space, and function by employing long-range systems to prevent friendly expeditionary maneuver from strategic and operational distances, and by employing direct and indirect fires from mid- and short-range systems to isolate and destroy forward deployed friendly forces.

[22] Christopher Paul and Miriam Matthews, *The Russian "Firehose of Falsehood" Propaganda Model* (Santa Monica, Calif.: RAND Corporation, 2016).
[23] A *fait accompli* attack is intended to achieve military and political objectives rapidly and then to quickly consolidate those gains so that any attempt to reverse the action by the U.S. would entail unacceptable cost and risk.

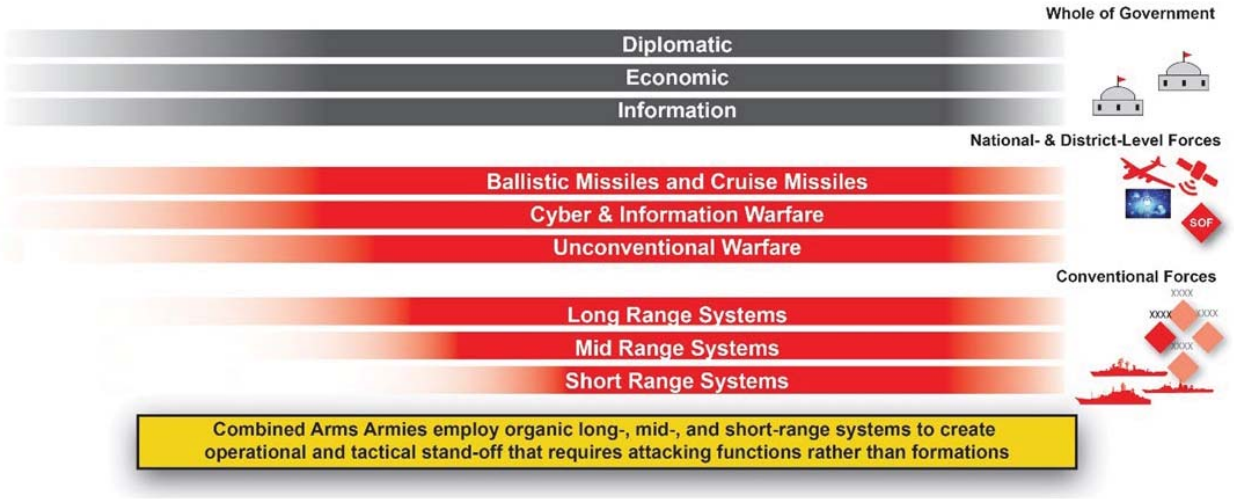

Figure 2-3. Adversary's layered stand-off

b. **Long-range fires systems.**

(1) Within Russian combined arms ground formations, long-range fires systems are carefully concealed from friendly ISR and well-protected by layered air defenses. In a continental theater, short-range ballistic missiles (SRBMs) and long-range SAM are the critical elements creating military stand-off, and are supplemented by long-range multiple rocket launchers (MRL), offensive cyber, counterspace, and unconventional warfare. Enemy long-range systems use intelligence gathered by SOF and espionage networks, space-based systems, unmanned aircraft systems (UAS), and ground-based sensors.

(2) The range of Russian long-range systems expands the battlefield into Support Areas. In conflict, the enemy will target U.S. command and sustainment capabilities to degrade friendly air and maritime superiority and reconnaissance, strike, and strategic lift.[24] Long-range kinetic strike capabilities will also target Army forward postured forces, prepositioned equipment, and munitions stocks. Russian offensive electronic warfare (EW), counterspace, and offensive cyber capabilities will jam, spoof, exploit, or destroy friendly space-based reconnaissance and communications platforms to prevent effective friendly mission command and ISR. Enemy long-range strike capabilities will also be used against civilian infrastructure and resources that support military operations, such as transportation networks, energy generation and distribution systems, and the defense industrial base.

c. **Mid-range and short-range systems.**

(1) Within Russian combined arms ground formations, mid-range systems provide the majority of fires. Advanced mid-range radars and SAM, capable of integration with long-range systems, pose a significant threat to friendly air forces. The weight of fire produced by standard MRL and cannon artillery employed in mass present the greatest danger to friendly ground forces, which can be destroyed before closing with enemy maneuver forces. Networked multi-

[24] Destroying integrated air defense systems (IADS) to facilitate deep strikes, isolating enemy maneuver forces, and opening the theater for friendly strategic movement are the critical initial premises of current Joint Force operations.

domain reconnaissance forces deployed in depth enable enemy mid-range fires. These forces consist of numerous ground observation teams, unmanned aerial systems, radars, and signal intercept units. Additionally, the enemy can commit offensive cyber, SOF, space-based, air strike, and maritime capabilities to reinforce combined arms ground maneuver formations when they are the main effort. Mid- and short-range air defenses severely limit friendly air surveillance capabilities, air assault, attack aviation, and close air support by forcing them to either operate at increased risk locally or with reduced effectiveness from stand-off ranges.

(2) Within the stand-off created by mid-range systems, enemy short-range systems (ground maneuver forces) maneuver to occupy key terrain, and create defensive positions that protect both the enemy long- and mid-range fires systems. In the offense, enemy short-range systems are designed to find and fix friendly forces to be destroyed by their long- and mid-range fires. Once in defensive positions, Russian combined arms ground formations employ camouflage, concealment, and decoys to defeat Joint Force surveillance and reconnaissance.

d. **Unconventional warfare.** Unconventional warfare activities support Russian conventional forces in armed conflict with reconnaissance, direct action strikes, and support in consolidating gains. Unconventional warfare capabilities play an important role in attacking friendly Support Areas by performing reconnaissance and direct action.

e. **Information warfare.** The actions of Russian conventional, national- and district-level capabilities, and unconventional warfare enable and empower its information narrative. The information narrative targets friendly leaders, populations, and forces. The effectiveness of the Russian information narrative in undermining friendly will is enhanced greatly by the success of its conventional forces.

f. **National- and district-level capabilities.** National- and district-level capabilities support Russian conventional forces in armed conflict by performing reconnaissance, disrupting the Joint Force's strategic and operational maneuver, and preventing a deliberate counteroffensive. Nuclear forces, information warfare, cyber capabilities, cruise missiles, space-based platforms, and special operations teams provide Russia a variety of options to threaten U.S. and partner homelands outside of the range of most conventional forces. Russia uses (or threatens to use) these capabilities to isolate the theater and to transition to consolidation operations after its conventional forces have accomplished objectives.

g. **Summary of Russian systems in conflict.** Russian long- and mid-range fires systems are its operational center of gravity in armed conflict. These systems create stand-off that enables a successful *fait accompli* attack. Russia employs these systems to destroy friendly forces' high-value capabilities, including headquarters, aircraft, and trained combat formations that are difficult to regenerate and essential to achieving U.S. operational and strategic objectives. Destroying these friendly high-value capabilities strengthens Russian information narratives and creates time and space to consolidate operational gains on political terms favorable to Russia.

2-4. Russia's consolidation operations in competition, armed conflict, and return to competition

a. Russian forces begin consolidation operations during armed conflict and continue these into the return to competition. During consolidation operations, Russia regenerates and re-postures military capacity while preserving any political gains achieved in conflict. If consolidation operations occur in a situation in which the Joint Force and partners have achieved a military advantage, the use or threat of Russian nuclear systems becomes an important element in maintaining its gains.

b. The information narrative is the main effort in Russian consolidation operations during the return to competition. The information narrative legitimizes gains while projecting the image of sustained military strength. In a supporting effort, unconventional warfare, conventional forces, and security forces extend control in enemy territory, eliminating dissent and blocking friendly information narratives from reaching the population or its own forces. Remaining Russian reconnaissance capabilities continue to operate in U.S. and partner territories. Russian ground forces enable its control over territory by destroying any friendly SOF and irregular capabilities.

c. Weapons of mass effect provide military stand-off during the return to competition, which allow Russia to regenerate and reposition military capabilities and consolidate gains. The combination of weapons of mass effect, information warfare, unconventional warfare, and proxies allows Russia to continue contesting the Joint Force in the return to competition, even if its conventional forces are severely degraded. This stand-off creates time and space for defeated enemy forces to reorganize and limits the extent to which the Joint Force can exploit operational military advantage.

2-5. Systemic vulnerabilities and dependencies

a. Russia's military exhibits patterns and vulnerabilities that can be exploited by changes to Joint Force operations, force posture, and capabilities. Russia:

(1) Uses information warfare (enabled by cyber) and conventional military forces in ways that, when exposed, galvanize rather than separate the U.S. and its allies.

(2) Organizes and operates forces through highly centralized command and control structures that have difficulty adapting to rapid tactical changes or complexity.

(3) Cannot accept high attrition to elite formations or key integrated air defense systems (IADS) and fires systems.

(4) Depends on achieving air superiority from the ground to protect its fires systems.

(5) Relies on a limited number of long-range strike systems and enabling munitions.

(6) Operates in territory and among populations in part or wholly friendly to the U.S.; therefore, the revisionist power faces constrained freedom of access in competition and will be contested in conflict.

(7) Possesses limited ability to reconstitute space-based assets.

b. The Chinese and Russian militaries are powerful, but they also have vulnerabilities that MDO seek to exploit. Both China and Russia are fielding mutually supporting systems designed to be effective against the well-understood patterns, posture, and capabilities of the current Joint Force. Altering Joint Force operational patterns and force posture will mitigate existing capacity and capability gaps and create opportunities to exploit Chinese and Russian operational shortfalls. The militaries of China and Russia have and will continue to have finite capacity of critical capabilities. The Joint Force's demonstrated capability to destroy or defeat these critical capabilities would prevent China and Russia from accomplishing objectives in competition, succeeding in armed conflict, or effectively transitioning to consolidation operations.

2-6. Other threats in the operational environment

The *U.S. Army in Multi-Domain Operations* concept applies to threats other than China and Russia. North Korea and Iran also seek to create political and military stand-off in order to achieve their strategic goals by destabilizing regional security. In some instances, North Korea and Iran directly employ or further proliferate Chinese and Russian anti-access and area denial capabilities to create military stand-off. Additionally, these countries employ indigenously developed capabilities or strategies to create stand-off. The Joint Force, therefore will also employ MDO adapted for the unique cultural, geographic, and military context against these and other future threats.

2-7. Implications for Multi-Domain Operations (MDO)

The common aspect among the current and emerging threats described in this chapter is the intent and capability to challenge the U.S. by employing a variety of means to generate stand-off that exploits political ambiguity and the strategic posture and operational predictability of the Joint Force. The current conceptual framework of the Joint Force and the Army does not account for the problem of stand-off, nor does it acknowledge the need to compete below the threshold of armed conflict against a near-peer adversary to expand the competitive space for policymakers. Countering these threats will require an operational concept that integrates capabilities from all domains, the EMS, and the information environment to offer solutions to a wide array of problems in both competition and armed conflict.

Chapter 3
Conducting MDO

3-1. Military problem

a. How does the Army enable the Joint Force to compete with China and Russia below armed conflict, penetrate and dis-integrate their anti-access and area denial systems and ultimately defeat them in armed conflict and consolidate gains, and then return to competition?

b. Solving the overarching military problem requires Army forces to address five problems posed by China and Russia in competition and conflict (see figure 3-1).

#1 How does the Joint Force compete to enable the defeat of an adversary's operations to destabilize the region, deter the escalation of violence, and, should violence escalate, enable a rapid transition to armed conflict?

#2 How does the Joint Force penetrate enemy anti-access and area denial systems throughout the depth of the Support Areas to enable strategic and operational maneuver?

#3 How does the Joint Force dis-integrate enemy anti-access and area denial systems in the Deep Areas to enable operational and tactical maneuver?

#4 How does the Joint Force exploit the resulting freedom of maneuver to achieve operational and strategic objectives through the defeat of the enemy in the Close and Deep Maneuver Areas?

#5 How does the Joint Force re-compete to consolidate gains and produce sustainable outcomes, set conditions for long-term deterrence, and adapt to the new security environment?

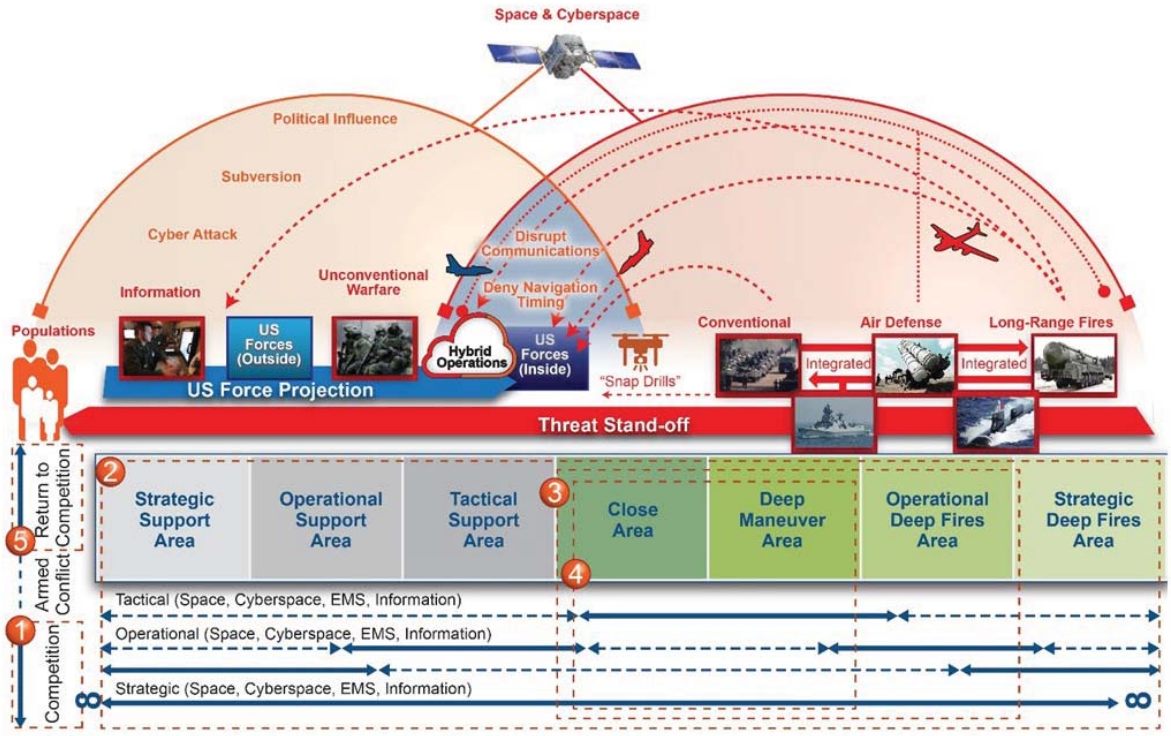

Figure 3-1. Problems superimposed on the MDO framework

3-2. Central idea
Army forces, as an element of the Joint Force, conduct MDO to prevail in competition; when necessary, Army forces penetrate and dis-integrate enemy anti-access and area denial systems and exploit the resultant freedom of maneuver to achieve strategic objectives (win) and force a return to competition on favorable terms.

3-3. Tenets of MDO

a. MDO solves the five problems through the combined application of three tenets: calibrated force posture, multi-domain formations, and convergence.[25] The tenets are mutually reinforcing and common to all MDO, though how they are realized will vary by echelon and depend upon the specific operational situation. The employment of the tenets – particularly calibrated force posture and convergence – also enable the global integration of the Joint Force to counter China and Russia during competition and armed conflict.

b. **Calibrated force posture.** Calibrated force posture is the combination of capacity, capability, position, and the ability to maneuver across strategic distances. Calibrated force posture allows Army forces to support Joint Force objectives in competition; deters armed conflict by preventing adversaries from attempting a *fait accompli* attack on favorable terms; and enables friendly forces to quickly seize the initiative in large-scale combat operations by setting the theater for expeditionary forces. Accomplishing these tasks requires a dynamic mix of different types of forces that adapt and change as dictated by the strategic environment: forward presence forces (U.S. and partner, conventional and SOF), expeditionary forces (Army and joint units and capabilities), and national-level cyberspace capabilities, space-based platforms, and strike capabilities. The appropriate balance of capabilities across the Total Force provides cohesive, fully capable forward presence forces and expeditionary forces able to deploy within strategically relevant time periods. Those postured forces also require the appropriate authorities to operate in all domains, the EMS, and the information environment, particularly in competition. The ability of the Joint Force to rapidly and unpredictably present an adversary with different combinations of forces and capabilities expands the competitive space for the U.S. and helps deter aggression by complicating an adversary's ability to achieve local superiority. In the event of a conflict, the application of calibrated force posture positions the right mix of ready forces and capabilities so they can rapidly transition to combat operations, penetrate and dis-integrate enemy anti-access and area denial systems within days, and exploit the resultant freedom of maneuver to defeat the enemy within weeks rather than months.[26]

(1) **Forward presence forces.** Forward presence forces consist of Army forward deployed and rotational units and capability sets. Forward presence forces include a wide array of Army capabilities, but of particular value due to their role in competition and the transition to armed conflict are mission command, intelligence, fires, sustainment, security force assistance, civil affairs, psychological operations, and SOF. Forward presence forces also provide enhanced

[25] The components of the solution link to the National Defense Strategy goals for developing a more lethal force: "Forward force maneuver and posture resilience" and "Develop a lethal, agile, and resilient force posture and employment," *Unclassified Summary of the National Defense Strategy*, pg. 6, 7.
[26] Calibrated force posture aligns with the Global Operating Model described in the National Defense Strategy. The National Defense Strategy "contact force" is composed of forward presence forces. The "blunt force" is a combination of forward presence forces and early-entry expeditionary forces. The "surge force" is follow-on expeditionary forces that arrive after the outbreak of armed conflict.

interoperability with partners through their integration into existing structures for command and control, intelligence, targeting, and cyberspace that are difficult for expeditionary forces to establish in a crisis or conflict. The persistence of Army forward presence forces is a foundational element of dynamic employment of the Joint Force as it enables joint strategic maneuver with critical combat, sustainment, protection, and mission command capabilities.

(2) **Expeditionary forces.** Expeditionary Army forces are those formations ready to maneuver from the U.S. or other regions across strategic distances while in contact with the adversary's reconnaissance, long-range fires, space, and cyberspace capabilities. Forces that deploy by air either bring their equipment or draw prepositioned equipment and are ready to fight within days or a few weeks of alert. Expeditionary forces deploying by sea are ready to fight within weeks. Expeditionary forces may also have to conduct joint forcible entry operations in the absence of forward presence forces or to open an additional line of operation. In conflict, the speed and effectiveness with which expeditionary forces can deploy along contested lines of communications are heavily dependent on the preparation and support of forward presence forces, the Reserve Components, other Services, and partners.

(3) **National-level capabilities.** National-level capabilities include intelligence, cyberspace, space-based, and some kinetic strike capabilities normally controlled above the theater level. These capabilities complement forward presence and expeditionary forces with their unique effects, global reach, and rapid execution that require little or no physical movement. The scarcity of these resources and the potential for unintended consequences with their use might cause policymakers to retain authorities or permissions for their use. The extensive preparation required to use these resources must begin in competition, when U.S. forces develop detailed intelligence identifying specific vulnerabilities, gain or prepare to request required authorities, and train to use national-level capabilities.

(4) **Authorities.** To operate in all domains, the EMS, and the information environment, the lowest appropriate echelon of Army forces requires tailored authorities in three broad areas: access, surveillance, and employment.[27] In competition, they need access to and presence in geographic areas and military and civilian networks that enable them to operate in both competition and conflict. In armed conflict, Army forces must have authorities to employ capabilities such as electronic attack, offensive cyberspace and space measures, and lethal strikes, especially to support a rapid transition from competition to conflict. In both competition and conflict, authorities to operate in the cyberspace domain and information environment must be granted earlier, faster, and to lower echelons to enable MDO. Forward presence headquarters enable success in both competition and the transition to armed conflict by making necessary coordination and lowering barriers to obtaining authorities before they are needed. Tailored authorities must also enable the Army's role as a force provider, with particular focus on authorities to notify and mobilize planned and contingency Reserve Component forces, formations, and headquarters.

[27] Examples of authorities include country team permissions for physical and virtual access (e.g., overflight permissions, access agreements, convoy clearances, materiel and non-materiel host nation support, ability to use or block segments of the EMS, and ability to employ offensive cyberspace operations), the ability to task transportation assets and forces for deployment, authority to obligate funds, and authority to conduct cross-boundary coordination.

c. **Multi-domain formations.** Multi-domain formations possess the combination of capacity, capability, and endurance which generates the resilience necessary to operate across multiple domains. All Army formations must be multi-domain capable to some degree. Multi-domain formations can conduct independent maneuver, employ cross-domain fires, and maximize human potential. The most important materiel contributors to resilience are advanced protection systems, reduced signatures, redundant channels for communications hardened against enemy interference, multiple sustainment networks, robust maneuver support capability and capacity, layered air defense, layered reconnaissance, and multi-domain obscuration capabilities. The most important non-materiel contributors to resilience are flexible planning that account for enemy actions, the ability to reorganize formations in conflict, leaders and staffs capable of operating in accord with intent, and small, dispersed, cross-trained headquarters. These combined contributors provide the resilience necessary for Army formations and systems at all echelons to conduct both offensive and defensive operations in contested spaces against a near-peer adversary.

(1) **Conduct independent maneuver.** Multi-domain formations conduct independent maneuver by continuing operations in a contested environment within the intent of the theater campaign.[28] Independent maneuver alludes to formation possessing the capacity, capability, and empowered initiative to operate under the constraints of the operational environment. Multi-domain formations possess organic capabilities to sustain and protect themselves until they regain contact with adjacent and supporting units. They are enabled by capabilities such as reduced visual and electromagnetic signatures, redundant channels for communications hardened against enemy interference, reduced logistics demand, enhanced medical support, multiple sustainment networks, robust maneuver support capability and capacity, and multi-domain obscuration capabilities. Brigades, divisions, and corps, specifically, require organic mission command, ISR, and sustainment capabilities to maintain offensive operations for several days despite highly contested lines of communications.

(2) **Employ cross-domain fires.** The ability to employ cross-domain fires provides options to commanders and builds resilience within the Joint Force to overcome temporary functional separation imposed by enemy anti-access and area denial systems. Beyond modernized air and missile defense and long-range ground fire capabilities, multi-domain formations deliver cross-domain fire capabilities through aviation systems; advanced protection systems, layered air defense and reconnaissance, EW devices; multi-spectral sensor-fused munitions; and cyberspace, space, and information related capabilities. Cross-domain fires include the ISR capabilities required to employ them, which can comprise a mixture of organic capabilities and access to external assets. Cross-domain fires combine with necessary advancements in mobility and lethality in future air and ground platforms, communications networks, and data processing (speed and volume) to provide the capabilities for cross-domain maneuver.

(3) **Maximize human potential.** The Army builds and sustains multi-domain formations through the selection, training, and education of the leaders and Soldiers in them. Advances in

[28] Independent maneuver is operating dispersed for an extended period without continuous [or contiguous] support from higher echelons while retaining the ability to concentrate combat power rapidly at decisive spaces by employing cross-domain fires and maneuver to achieve mission objectives within the intent of the theater campaign.

performance science enable Soldiers and junior leaders to enter operations at peak cognitive, physical, and emotional potential. Biotechnical sensors monitoring the status and changes in human performance augment commanders' understanding of their units, inform decisions about the tempo and intensity of operations, and assist units in sustaining and regenerating physical and psychological strength. Man-machine interfaces, enabled by artificial intelligence and high-speed data processing, improve human decision making in both speed and accuracy. Employing multi-domain capabilities requires the Army to attract, train, retain, and employ leaders and Soldiers who collectively possess a significant breadth and depth of technical and professional expertise. The Army must exercise careful talent management to make the most of these high-quality personnel and integrate them into trusted teams of professionals who are able to thrive in ambiguity and chaos. Improving the resilience of leaders and Soldiers—the Army's most valuable capability—requires training, educating, equipping, and supporting them to execute MDO in all of its intensity, rigor, and complexity.

d. **Convergence.** Convergence is the rapid and continuous integration of capabilities in all domains, the EMS, and the information environment that optimizes effects to overmatch the enemy through cross-domain synergy and multiple forms of attack all enabled by mission command and disciplined initiative. The Joint Force currently converges capabilities through episodic synchronization of domain-federated solutions. Future operations against a near-peer threat, however, will require the Joint Force to conduct continuous and rapid integration of multi-domain capabilities to gain cross-domain overmatch at decisive spaces. Decisive spaces are locations in time and space (physical, virtual, and cognitive) where the full optimization of the employment of cross-domain capabilities generates a marked advantage over an enemy and greatly influences the outcome of an operation. Convergence complicates the enemy's attempts to conceal and defend its center of gravity by providing the Joint Force with multiple options for attacking the enemy's vulnerabilities at decisive spaces. Multi-domain formations, at echelon, utilize convergence during competition and conflict to apply capabilities against vulnerabilities in an adversary's or enemy's systems.

(1) Convergence has two advantages over single-domain alternatives: the creation of cross-domain synergy and the layering of options across domains to enhance friendly operations and impose complexity on the enemy. Through convergence, multi-domain capabilities are brought together in stimulate-see-strike or see-strike combinations that disrupt, degrade, destroy, or dis-integrate enemy systems or create windows of superiority to enable friendly exploitation of the initiative.

(a) **Cross-domain synergy.**[29] The principle of cross-domain synergy is an evolution of combined arms maneuver. The combination of complementary effects complicates an enemy's ability to act, producing an overall effect greater than the sum of the individual parts (see figure 3-2). Synergy optimizes capabilities from across all domains, the EMS, and the information environment to achieve the maximum effect from the available resources. Against a near-peer enemy, the Joint Force will not have sufficient capacity to achieve overmatch without cross-domain synergy.

[29] Cross-domain synergy is an idea introduced in the Joint Operational Access Concept and continued as a key idea in the Capstone Concept for Joint Operations. It is defined as the complementary vice merely additive employment of capabilities in different domains such that each enhances the effectiveness and compensates for the vulnerabilities of the others to establish superiority in some combination of domains that will provide the freedom of action required by the mission.

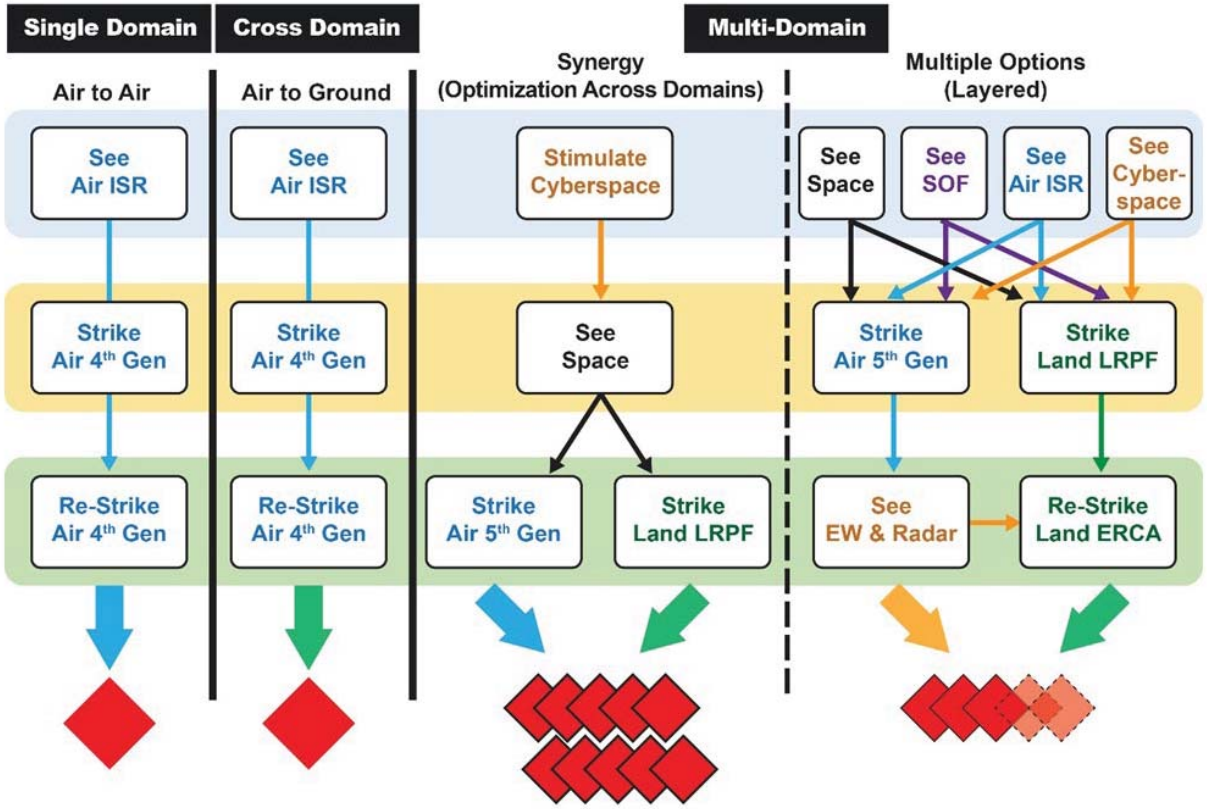

Figure 3-2. Converging capabilities to generate cross-domain synergy and layered options

(b) **Layered options.** The layering of multiple forms of convergence provides friendly commanders with options and imposes complexity on the enemy (see figure 3-2). The creation of additional options makes it easier for friendly forces to target enemy vulnerabilities in unexpected ways and avoids dependence on a single method of seeing or striking. Layered options also confront the enemy with an array of different threats to which it must respond. So long as those convergence combinations are relatively simple for friendly forces to execute, the result is a net imposition of complexity upon enemy command and control systems.

(2) **Mission command.** Mission command remains an essential element of Army operations on a contested battlefield against a near-peer enemy. Since the enemy will disrupt friendly communications and plans, mission command must expand to enable initiative and dynamic cooperation across Service and other partner lines—at some risk—to allow the Joint Force to preserve the ability to continuously and rapidly integrate multi-domain capabilities despite disrupted communications. One manifestation of mission command is *intent-based synergy*, the dynamic cooperation that enables the sufficient integration of available cross-domain capabilities to achieve dominant or essential effects at a decisive space, acknowledging some degree of risk or collateral cost. Commanders must deliberately create and foster conditions favorable to mission command so that ever disparate formations and capabilities are ready to act upon mutual recognition of an opportunity or in response to a battlefield development.

(3) **Convergence at echelon.** Multi-domain formations and calibrated force posture enable convergence. The principles of convergence apply across echelons, but vary based on specific requirements.

(a) **Theater army.** Theater armies are forward presence forces. They enable interagency access, set the theater, enable expeditionary maneuver, and protect joint bases, nodes, and networks. Theater armies set the conditions for operational and tactical convergence by calibrating force posture with Combatant Commands, the Joint Staff, and Headquarters, Department of the Army to ensure that necessary joint and Army capabilities are in theater or can be accessed when and where needed to deter or defeat aggression. Theater armies converge offensive space control capabilities on behalf of all Army forces in theater. Theater armies are also the main Army echelon converging capabilities to support joint and combined information environment operations.

(b) **Field army.** Field armies are forward presence forces in regions that have near-peer threats. They relieve the operational burden on theater armies to facilitate focused opposition toward that specific threat within a distinct area of operations. They prosecute the campaign in competition by conducting intelligence preparation of the battlefield (IPB), enabling partners and SOF, deterring the adversary's aggression, and managing the transition to conflict. They have the ability to command two or more corps. The field army provides long-range fires to other component commanders against enemy long-range systems. In competition, the field army oversees deception, the selective demonstration of capabilities, and the masking of others to create uncertainty and deter an adversary's aggression. The field army also creates options for convergence through focused planning and preparation for multi-domain interoperability with partners. The field army converges capabilities to destroy enemy long-range ground fires and, if no corps headquarters is present during the transition to armed conflict, will assist with the targeting and neutralization of mid-range systems. In competition and conflict, the field army is the Army echelon responsible for converging national-level capabilities into its or subordinate echelons' maneuver. In competition and conflict, the field army is responsible for analyzing high-volume data from national and theater intelligence collection assets, and linking sensors to specific shooters in support of operational ground objectives. Intelligence enabling formations at the field army level will be task organized and tailored to the operational environment.

(c) **Corps.** Corps are expeditionary forces. The corps shapes multiple enemy combined arms armies simultaneously by assisting with the defeat of long-range systems and the neutralization of mid-range systems. The corps also commands two or more divisions and enablers. It is responsible for converging capabilities against all enemy long-range systems (air defense, anti-ship, and long-range ground fires) within areas designated by the Joint Force Commander and providing Army capabilities to assist other components when the corps is responsible for multi-domain command and control. A corps converges capabilities against enemy mid-range fires formations within its areas of operations. The corps is the Army echelon responsible for converging large amounts of joint fires, whether against enemy mid-range systems or in support of division or brigade maneuver. The corps also converges national- and theater-level offensive cyberspace with other capabilities to achieve operational and tactical objectives. The corps creates conditions for convergence at lower echelons by allocating resources, sequencing division maneuver, and incorporating it with deception. In competition

and conflict, a corps conducts intelligence analysis to converge national, theater, and organic ISR collection to support tactical ground objectives.

(d) **Division.** Divisions can be either forward presence or expeditionary forces. A division enables independent maneuver, conducts expeditionary maneuver, commands multiple brigade combat teams and enabling brigades, and defeats a shaped enemy army in the Close Area. It converges aviation, fires, EW, maneuver support, and multi-brigade maneuver to achieve positions of advantage against a combined arms army (or similar formation) that has had its mid-range fires systems destroyed or neutralized. The division has the multi-domain command and control capacity to incorporate some reinforcing joint or Army fires when it is a secondary effort. A division that is the main effort and has been allocated a large number of air sorties, a significant amount of naval strikes, or several brigades of reinforcing ground fires requires assistance from the corps to converge capabilities on that scale. With assistance from higher echelons, the division can converge national-level and offensive space capabilities into its scheme of maneuver. A division has the analytical capacity to converge limited amounts of national- or theater-level intelligence sources with its organic ISR.

(e) **Brigade.**[30] Brigades converge organic ISR, maneuver, and fires capabilities with limited amounts of available aviation, maneuver support, EW, joint fires, and offensive space capabilities. All brigades are multi-domain capable, yet those responsible for controlling terrain require high levels of cross-domain organic capabilities to create the convergence that enables their broader task sets. Brigades habitually access intelligence, EW, cyberspace, and space capabilities through the division, corps, and field army as described above. Brigades execute convergence and cross-domain maneuver to see, isolate, maneuver, and/or protect to exploit the initiative and achieve positions of advantage to accomplish their missions. A brigade has the analytical capacity to converge limited amounts of national- or theater-level intelligence sources with its organic ISR.

e. **Multi-domain command and control.** Interoperability across Service, interagency, and multinational partners is a key element to executing MDO. Multi-domain command and control is the combination of joint and combined materiel, processes, and authorities that underpin convergence, multi-domain formations, and mission command designed to enable and exploit interoperability.[31] Effective multi-domain command and control requires a resilient technical architecture, flexible command relationships, and multi-domain control measures. A resilient technical architecture provides connectivity to pass critical information between headquarters, units, aircraft, or ships at critical moments in operations. Flexible command relationships allow the rapid reallocation of multi-domain capabilities and formations across functional components and echelons to achieve convergence. Flexible command relationships also allow the creation of favorable force ratios through rapid task organization and re-organization of reinforcing fires and capabilities among echelons. Multi-domain control measures create the framework for mission command by allowing units the greatest possible latitude to execute cross-domain maneuver within intent. Multi-domain control measures also facilitate coordination between echelons,

[30] This includes all types of brigade-level formations, not only Brigade Combat Teams.
[31] North Atlantic Treaty Organization Allied Joint Publication 01(D), Allied Joint Doctrine, describes the three dimensions of joint and allied interoperability – technical (e.g., hardware, systems) procedural (e.g., doctrines, procedures), and human (e.g., language, terminology, and training). These directly align to the technical architecture, control measures, and command relationships in multi-domain command and control.

adjacent units, and joint partners. When technical architecture is disrupted, flexible command relationships and multi-domain control measures are the enabling elements of mission command.

3-4. MDO and strategic objectives

a. The *U.S. Army in Multi-Domain Operations* is an operational-level military concept designed to achieve U.S. strategic objectives articulated in the *National Defense Strategy,* specifically deterring and defeating China and Russia in competition and conflict.[32] The concept also supports execution of the Army's four enduring strategic roles: prevent conflict, shape the security environment, prevail in large-scale ground combat operations, and consolidate gains. These strategic objectives require Army forces to solve the five multi-domain problems described in section 3-1. The following sections describe how MDO solves each of these problems. Section 3-5 addresses the first problem of competing to defeat aggression short of armed conflict and to deter conflict. Section 3-6 addresses the second problem of penetrating enemy anti-access and area denial systems to enable strategic and operational maneuver in conflict. Section 3-7 addresses the third problems of dis-integrating enemy's anti-access and area denial systems in theater to enable operational and tactical maneuver. Section 3-8 addresses the fourth problem of exploiting freedom of maneuver to defeat the enemy and achieve U.S. strategic objectives. Section 3-9 addresses the final problem of re-competing to consolidate gains and expand the competitive space and enable policymakers to resolve the conflict. The remainder of this section describes how solving these operational problems leads to the attainment of strategic objectives.

b. A multi-domain capable Joint Force can achieve friendly strategic objectives (win) and defeat the adversary in three different ways. The preferred method of attaining strategic objectives is effective competition that deters escalation and defeats adversaries' destabilization efforts. If deterrence fails, the second method is to employ a combination of forward presence and expeditionary forces to deny enemy objectives within days and achieve an operational position of relative advantage within weeks that leads to an acceptable, sustainable political outcome. If neither side is able to achieve its objectives in a short conflict, the third method is to defeat the enemy in a protracted war. The three methods are interrelated as the will and capability to win a long war, if necessary, is an essential element to convincing an adversary that it cannot achieve a *fait accompli* and will not achieve aims in competition below armed conflict. The demonstrated ability and readiness to deny a *fait accompli* attack, in turn, creates a position of strength for the Joint Force in competition. The Army is essential in each of the three ways to defeat an aggressive adversary and provide political leaders with as many options as possible to deter through determined competition or, when necessary, prosecute and end an armed conflict on favorable conditions before returning rapidly to a renewed competition.

c. **Compete.** The Joint Force succeeds in competition by defeating the adversary's efforts to achieve their strategic goals and deterring military escalation; it does this by expanding the competitive space for policymakers through multiple options for employing the elements of

[32] U.S. Department of Defense, *Summary of the 2018 National Defense Strategy of the United States of America: Sharpening the American Military's Competitive Edge,* https://www.defense.gov/Portals/1/Documents/pubs/2018-National-Defense-Strategy-Summary.pdf.

national power.[33] Army forces play an integral role in this effort, actively engaging across domains (including space and cyberspace), in the EMS, and in the information space. The demonstrated capability to prevail in competition and in conflict counters adversaries' narratives that portray the U.S. as a weak or irresolute partner. The combination of the ability to both effectively compete below armed conflict and to respond to an escalation toward armed conflict creates a position of strength and sets favorable conditions if conflict ensues. This position of strength provides a favorable environment for Joint Force, interagency, and partner efforts to counter adversaries' coercion through unconventional and information warfare. The adversary's proxies receive little or no support from its conventional forces, which allows U.S. partners to counter attempts to destabilize their countries more easily. The combined and persistent effects of deterring armed conflict and defeating unconventional and information warfare in a campaign of competition create unpredictability for the adversary and generate additional friendly options, thereby expanding the competitive space for policymakers.

d. **Penetrate, dis-integrate, and exploit.** In the event of armed conflict, Army forward presence and expeditionary forces enable the rapid defeat of aggression through a combination of calibrated force posture, multi-domain formations, and convergence to immediately contest an enemy attack in depth. Army long-range fires converge with joint multi-domain capabilities to penetrate and dis-integrate enemy anti-access and area denial systems to enable Joint Force freedom of strategic and operational maneuver. Within the theater, Army forces converge capabilities to optimize the employment of capabilities from across multiple domains against critical components of the enemy's anti-access and area denial systems, specifically long-range air defense and fires systems. Convergence against the enemy's long-range systems enables the initial penetration. This sets the conditions for a quick transition to joint air-ground operations in which maneuver enables strike and strike enables maneuver. MDO in the Close and Deep Areas combine fires, maneuver, and deception to dislocate the enemy defense by physically, virtually, and cognitively isolating its subordinate elements, thereby allowing friendly forces to achieve local superiority and favorable force ratios. Army forces, having penetrated and begun the dis-integration of the enemy's anti-access and area denial systems, exploit vulnerable enemy units and systems to defeat enemy forces and achieve friendly campaign objectives. As part of the Joint Force, Army forces rapidly achieve given strategic objectives (win) and consolidate gains.

[33] Expanding the competitive space entails those activities, short of war, that integrate multiple elements of national power to counter the long-term strategic objectives of adversaries. A more lethal force, strong alliances and partnerships, American technological innovation, and a culture of performance generate decisive and sustained U.S. advantages. See, *Summary of the 2018 National Defense Strategy of the United States of America*, 4.

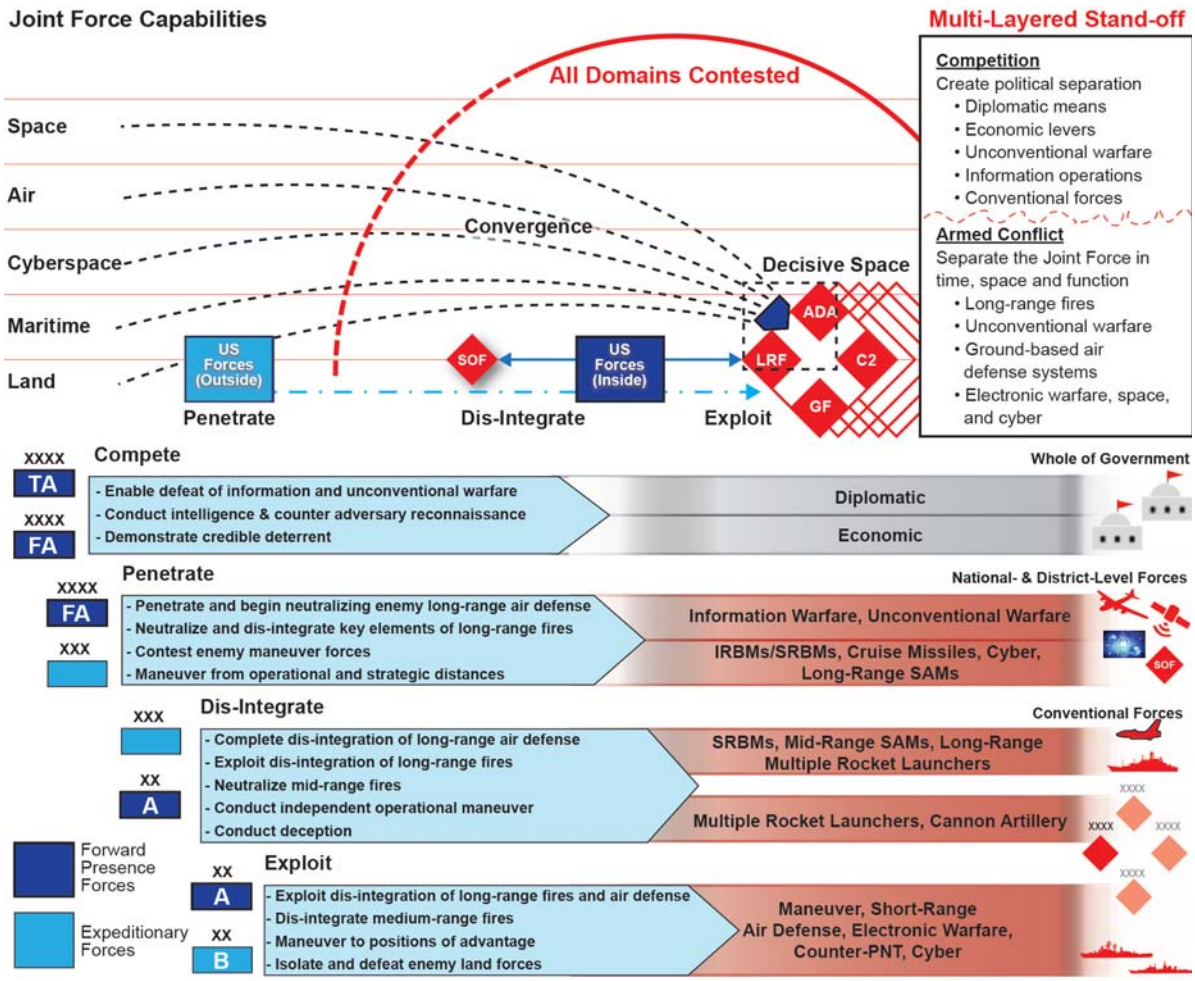

Figure 3-3. MDO solutions

e. **Re-compete.** Army forces contribute to the consolidation of strategic gains after a conflict by securing the initiative and maintaining operational contact in all domains, the EMS, and the information environment. This approach ensures that military and political conditions remain favorable to the U.S. and its partners. Particularly following an armed conflict with a nuclear power, the enemy will retain significant conventional military capability in the field. Army forces, therefore, have to simultaneously deter a return to conventional warfare and assist partner forces in restoring order to prevent the enemy from exploiting the internal disruption for strategic advantage.[34] These functions spanning the competition continuum expand the competitive space for policymakers, enable strategic objectives, and secure the initiative.[35]

[34] In most cases, the Army will be required to execute tasks to restore order and support partner's political, economic, and social structure recovery (per FM 3-07 *Stability*) because civilian agencies lack the capacity or capability to do this in a combat zone.
[35] The Joint Concept for Integrated Campaigning proposes the notion of a *competition continuum* that offers an alternative to the obsolete peace/war binary with a new model of cooperation, competition below armed conflict, and armed conflict. These are not mutually exclusive conditions and various states of relationships with other actors can exist concurrently. This concept focuses on conditions of competition and armed conflict.

3-5. MDO in competition: Compete to expand the competitive space

a. Multi-domain problem #1: How does the Joint Force compete to defeat an adversary's operations to destabilize the region, deter the escalation of violence, and, should violence escalate, enable a rapid transition to armed conflict?

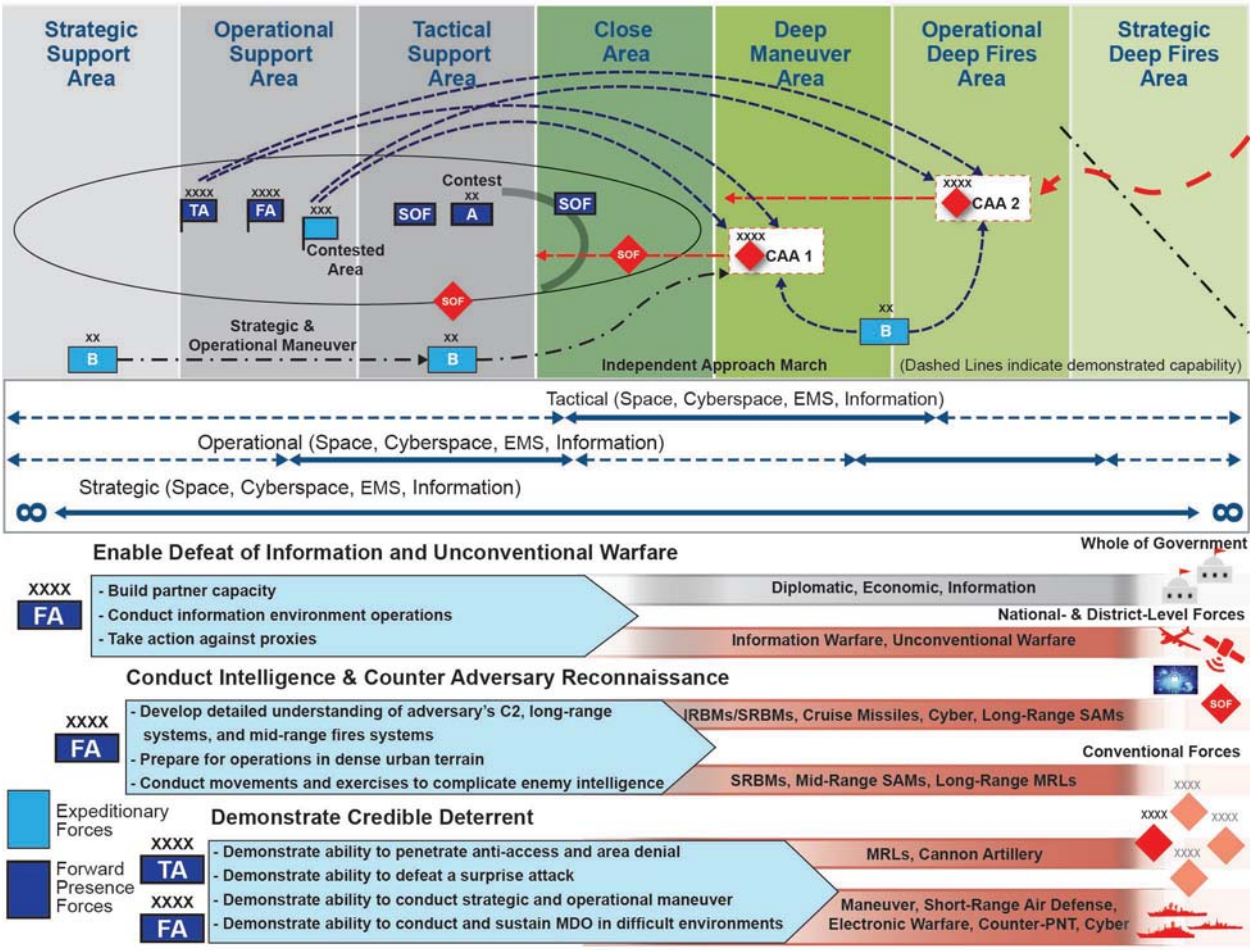

Figure 3-4. Competition

b. Success in competition achieves three critical objectives: deterring conflict on terms favorable to the U.S., countering adversaries' efforts to expand the competitive space below the threshold of armed conflict, and enabling the rapid transition to armed conflict. In the past, the U.S. military—due to cultural, statutory, and policy reasons—has often remained reactive in competition below armed conflict. The *U.S. Army in Multi-Domain Operations* concept emphasizes the importance of active engagement by the Joint Force, and particularly the Army, in competition to defend U.S. interests, deter conflict, and, when needed, create the most favorable conditions for the Joint Force's rapid transition to armed conflict.

c. The Army competes successfully, as part of a joint, interagency, and multinational team, by defeating the adversary's attempts to destabilize regional security and by deterring armed conflict through a series of mutually reinforcing actions. The field army conducts detailed tactical and operational intelligence preparation of the battlefield to enable forward presence and

expeditionary forces to immediately defeat a surprise attack by the adversary. In conjunction with partners and the Joint Force, Army forces counter the adversary's reconnaissance and conduct deception to create uncertainty within an adversary's decision making process. Forward presence forces also contribute to the defeat of the adversary's unconventional warfare campaign, both directly and indirectly, both by enabling partners with advisors and capabilities and by building enduring partner capability and capacity. These formations, enabled by the necessary authorities, actively engage in the information space through a variety of means, including cyberspace and EMS capabilities. Finally, both the theater and field army conduct intensive preparations for conventional warfare to demonstrate a credible deterrent. The theater army sets the theater to enable the dynamic employment of the Joint Force. The field army "sets the campaign" to ensure the Joint Force and partners can rapidly transition from competition to conflict.

d. **Conduct intelligence and counter adversary reconnaissance.** In competition, the field army coordinates collection against and analysis of the adversary's operational and tactical systems, as well as other facets of the operational environment and civil networks. Subsequently, the field army disseminates information to allocated joint and Army expeditionary forces to familiarize them with the adversary's systems and likely areas of joint and Army operations. The field army also has the primary responsibility for countering the adversary's reconnaissance through counter-reconnaissance and deception. Collectively, these actions enable the Joint Force to rapidly transition to armed conflict and create uncertainty for the adversary as to whether it can achieve its objectives through a surprise attack.

(1) **Develop understanding of military capabilities.** The complexity of modern military equipment requires months or years of focused intelligence collection and analysis to identify and exploit tactical or technical weaknesses. The field army works primarily with theater- and national-level capabilities to develop a detailed understanding of the adversary's command and control and long-range (IADS, SRBM, and long-range MRL) and mid-range systems (mid-range SAM, MRL, and cannon artillery). When the adversary's forces conduct maneuvers or "snap exercises" near territory of U.S. partners, the field army deploys organic and allocated ISR (e.g., airborne ISR, high-altitude ISR balloons, and electronic intelligence capabilities) to refine technical intelligence and to understand the adversary's operational patterns and methods of employment by specific unit and capability. The field army also seeks to create intelligence collection opportunities by leveraging training and reassurance operations in partner territory adjacent to an adversary to stimulate and analyze enemy ISR capabilities.

(2) **Analyze operational environment and civil networks.** All echelons of forward presence forces conduct terrain analysis and familiarization of friendly territory threatened by an adversary. This effort builds the necessary information that allows the Joint Force Commander to visualize the three-dimensional, multi-domain environment at a level of detail for tactical execution and operational planning. Dense urban terrain requires additional preparatory intelligence activities to understand the human, social, and infrastructure details. The field army focuses IPB on select urban areas that are likely to be of critical of strategic and operational importance in conflict.

(3) **Conduct deception.** In competition, the theater and field armies conduct deception primarily through dynamic changes to calibrated force posture. These actions seek to complicate the adversary's efforts to determine the capability and capacity of friendly forces in theater. While exercises, training, and alerts are designed to demonstrate specific capabilities, they also provide opportunities to mislead the adversary regarding the disposition and staging of forces, use of the EMS and cyberspace signatures, and patterns and methods of employment. These actions create unpredictability and complicate the adversary's reconnaissance efforts, which increases the likelihood of compromising its assets. The theater army also employs data encryption, network access limitations, and decoy data to defeat the adversary's cyber reconnaissance.

(4) **Execute counter-reconnaissance.** The field army conducts and coordinates counter-reconnaissance operations principally through partner security forces and interagency partners. Partner security forces generally possess the authorities, capacity, and local expertise to counter the enemy's covert intelligence efforts. The primary role of the field army, therefore, is to assist partner security forces with counter-reconnaissance operations. These actions reduce the tactical effectiveness of an adversary's efforts in competition and their ability to transition rapidly from competition to armed conflict.

e. **Enable defeat of the adversary's information and unconventional warfare.** Army forces support joint and partner campaigns to defeat the adversary's information and unconventional warfare operations through the provision of capabilities, expanded authorities, and the conduct of supporting operations.

(1) **Conduct information environment operations (IEO)**. The Joint Force seizes the initiative in competition by actively engaging in the information space across domains (to include cyberspace) and the EMS. The theater army converges Army actions and messaging in support of the Joint Force Commander's IEO, though all echelons engage in the information space in support of policy and commander's intent. To accomplish this mission, subordinate echelons must be enabled with access to intelligence, cyberspace, and EMS capabilities; appropriate authorities and permissions normally reserved for conflict or at higher echelons; and policy guidance expressed as intent rather than narrow, restrictive directives. This allows forward presence forces to aggressively take tailored actions and employ messages to counter and expose inconsistencies in the adversary's information warfare operations. The Army primarily contributes to the strategic narrative, however, by reinforcing the resolve and commitment of the U.S. to its partner and demonstrating its capabilities as a credible deterrent to conflict.

(2) **Conduct irregular warfare.**[36] The theater and field armies enable joint, interagency, and partner irregular warfare campaigns by providing multi-domain formations with regional understanding to the Joint Force Commander. When an adversary employs proxies, Army forces defeat them principally through the indirect enabling of partners, but can support directly through unilateral action. Special operations forces and security force assistance brigades support partner

[36] *Irregular warfare* is comprised of five core activities: counterinsurgency, counterterrorism, unconventional warfare, foreign internal defense, and stability operations.

irregular warfare efforts both by building enduring partner capacity and by enabling them with advisors and capabilities.

f. **Demonstrate credible deterrent.** By shaping the entire theater and addressing aggression outside the field army's area of operations, the theater army allows the field army to set the campaign against a near-peer adversary's military formations and stand-off capabilities. To provide a credible deterrent, the field army calibrates force posture to reduce an adversary's local military superiority, employs multi-domain formations to withstand a surprise attack, and demonstrates the ability to converge forward presence, joint, and national-level capabilities to disrupt any surprise attack. Specifically, Army forces must demonstrate four capabilities in competition to deter the adversary.

(1) **Ability to immediately deny a *fait accompli* attack.** The field army must be able to deny an enemy *fait accompli* attack within weeks by employing a mixture of forward presence, expeditionary (air deployed assets/formations and prepositioned equipment), and national-level forces.

(2) **Ability to penetrate anti-access and area denial systems.** Forward presence Army long-range fires must enable the Joint Force to immediately begin neutralizing enemy long-range systems (IADS, SRBM, long-range MRL, and command and control) and have munitions stockpiles in theater sufficient to support operations for several weeks.

(3) **Ability to conduct strategic and operational maneuver.** Army expeditionary forces must build and demonstrate the ability to conduct strategic and operational maneuver into an area of operations despite contested lines of communications.

(4) **Ability to support MDO.** Army forces have to calibrate force posture and field multi-domain formations to facilitate the Joint Force to dictate and sustain operational tempo in conflict. To credibly accomplish these tasks, the theater and field army establish command and control mechanisms, ensure interoperability, and sustain and protect forward presence forces.

(a) **Establish command and control mechanisms.** In competition, the field army prepares to converge lethal and nonlethal effects from the beginning of a conflict by planning with forward presence forces, other elements of the Joint Force, and partners. This preparation includes developing the necessary multi-domain command and control architectures, flexible command relationships, and physical and virtual control measures for converging capabilities. Precise and integrated effects are critical to operations in dense urban terrain, but also facilitate operations in other environments, particularly chemical, biological, radiological, or nuclear (CBRN) impacted zones.

(b) **Ensure interoperability.** Forward presence forces must be fully interoperable with the remainder of the Joint Force and, to the greatest extent possible, with multinational partners and relevant interagency partners. If a low degree of interoperability exists with a partner, Army forces integrate MDO through an array of doctrinal or ad hoc organizational methods, such as liaison cells. Increasing interoperability builds capacity and expands the range of options for the Joint Force Commander.

(c) **Sustain and protect forward presence forces.** The theater army ensures the Operational Support Area has the capacity, capability, and endurance to sustain and generate force despite the adversary's long-range fires (ballistic and cruise missiles, special operations, offensive space, and cyber attacks). The field army ensures the Tactical Support Area and Close Area possess the multi-domain formations needed to sustain and generate force despite the adversary's ballistic missiles, long-range MRLs, air defenses, and cyber attacks. The theater army creates resilience through the protection, hardening, and dispersal of key command, control, and logistics nodes. It also plans and coordinates for multiple sea and air ports of entry and lines of communication throughout the Operational and Tactical Support Areas.

g. **Conclusion: MDO in competition.** Army forces, as part of the Joint Force, compete with a near-peer adversary by defeating their operations below the threshold of armed conflict and deterring an escalation of violence. Army forces at all echelons support U.S. policy and objectives through proactive engagement in the information space, and are in turn enabled by delegated authorities and permissions, intent-based guidance, and access to joint and national-level capabilities in intelligence, cyberspace, and the EMS. The friendly information narrative is supported by the demonstrated capability to deny a *fait accompli* attack and an adversary's operational objectives. Demonstrated capabilities in competition undermine the adversary's information warfare operations and generate complexity and uncertainty in their decision making process. Most importantly, active engagement in competition establishes a robust operational assessment of the adversary's forces and capabilities and sets the campaign to ensure the Joint Force can rapidly transition to armed conflict and immediately provide an offensive response to aggression.

The three subsequent sections detail actions to penetrate stand-off, dis-integrate anti-access and area denial systems, and exploit the resulting freedom of action and maneuver. Although presented sequentially, each section's actions overlap in time and space to varying degrees. Because near-peer enemies have the ability to adapt, reorganize, and reconstitute their systems and formations, friendly forces continue penetration and dis-integration concurrent to maneuver to fully exploit windows of superiority.

3-6. MDO in armed conflict: Penetrate strategic and operational stand-off

a. Multi-domain problem #2: How does the Joint Force penetrate enemy anti-access and area denial systems throughout the depth of the operational framework to enable strategic and operational maneuver?

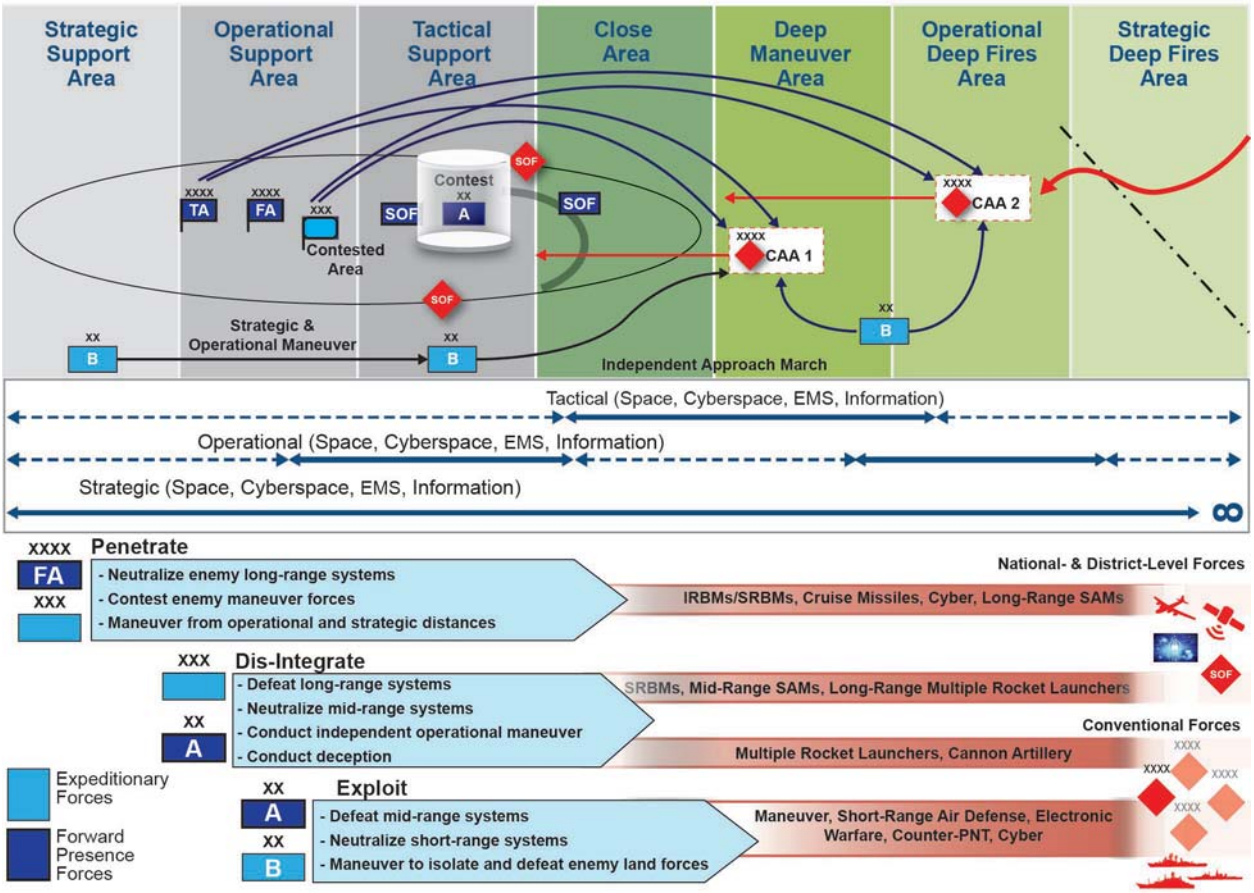

Figure 3-5. Penetrate and dis-integrate anti-access and area denial systems; exploit freedom of maneuver

b. The Joint Force utilizes the active engagement in competition to enable the penetration of strategic and operational stand-off by immediately neutralizing the enemy's long-range systems, contesting enemy maneuver forces in all domains, the EMS, and the information environment, and conducting strategic and operational maneuver. The neutralization of enemy long-range systems enables strategic and operational maneuver by reducing the threat to friendly lines of communications. Simultaneously, forward presence forces begin the defeat of enemy stand-off "from the inside" by operating within the range of enemy long- and mid-range systems. Together, these efforts effectively contest the enemy's attack; enable greater freedom to maneuver elements of the Joint Force from strategic and operational distances into the area of operations; and enable the dis-integration of the enemy's long- and mid-range systems in decisive spaces.

c. **Neutralize enemy-long-range systems.** Benefiting from extensive preparations during the competition period, forward positioned Army fires and air defense forces immediately begin neutralizing the enemy's long-range anti-access and area denial systems (ballistic and cruise missiles, long-range IADS) during the transition to armed conflict.

(1) The field army and corps employ long-range fires elements and integrate joint and combined capabilities to neutralize the enemy's long-range systems. Fires formations at those echelons provide responsive cross-domain fires to the Joint Force Commander into the Close, Deep Maneuver, and Operational Deep Fires Areas. In combination with other multi-domain capabilities, these fires begin to neutralize the enemy's integrated air defense and long-range fires systems. They accomplish this by receiving targeting information for high-priority enemy long-range systems from space- and high-altitude-based surveillance or low-observable air platforms, and striking those high-payoff targets within minutes (paragraphs 3-7.d and 3-7.e provide a more detailed description of how the enemy's long-range systems are identified and attacked).

(2) Ground-based long-range fires provide redundant strike options to the Joint Force, posing dilemmas for the enemy in multiple ways. Long-range ground fires offer a responsive strike capability (cued by intelligence within minutes), with the capacity to overwhelm point defenses and strike targets over larger areas. Long-range ground fires complicate enemy defenses by forcing the enemy to react to multiple forms of attack simultaneously against a number of different systems for which it does not have an effective counter. The Army's contribution of highly mobile and dispersed long-range fires systems also complicates the enemy's counterfire, reconnaissance, and targeting. By combining Army long-range fires with other multi-domain capabilities, the Joint Force increases the speed and scale of its efforts to neutralize the enemy's long-range systems.

d. **Contest enemy maneuver forces.** Forward positioned forces immediately contest the enemy attack by enemy maneuver forces. Depending on force posture and the amount of intelligence and warning, forward presence forces in the Close Area could vary in strength from a single brigade to an entire division of forward deployed, rotational, and expeditionary forces deployed by air prior to the conflict. When attacked, forward presence forces in the Close Area (partner territory that the enemy is attempting to seize), in concert with partner forces, impose losses on the enemy to delay its achievement of campaign objectives and consolidation of gains. Forward presence Army forces and partners employ layered ISR, both organic and joint, to develop an understanding of the enemy's attack and their capabilities. They also build on the counter-reconnaissance activities executed in competition to rapidly degrade enemy intelligence in the Close Area. The Joint Force Commander employs joint fires and national-level capabilities to assist forward presence forces denying enemy objectives in the Close Area and the field army executes IEO contingency plans to rapidly seize the initiative in the information environment.

(1) **See with layered ISR.** U.S. and partner forces in the Close Area employ a layered ISR network to determine the disposition of enemy forces. The layered ISR network provides redundancy against the enemy's ability to contest friendly ISR assets and facilitates layered collection and dissemination.

(a) **Layered collection plan.** Forward presence divisions and brigades employ their organic ground reconnaissance and UAS to develop the immediate tactical situation. The field army primarily relies on organic high-altitude surveillance and joint ISR capabilities deployed from the forward edge of the Tactical Support Area, supplemented by low-observable manned and unmanned aircraft, space surveillance, and cyberspace intelligence. The field army also utilizes an existing intelligence, surveillance, and reconnaissance network developed with partners during competition that consists of overlapping systems of remote and autonomous sensors, human intelligence, and friendly special operations forces.

(b) **Processing and dissemination.** The field army uses standard and non-standard communications methods to rapidly process and disseminate intelligence to maneuver forces in the Close Area and to sustainment and protection forces in the Tactical Support Area. The field army analyzes the intelligence and disseminates time sensitive combat information to the division and the brigades using resilient, low-density data formats to mitigate significant enemy jamming and counter-communications attacks. The field army also establishes sensor-to-shooter links to enable cross-domain fires in support of subordinate operations.

(2) **Degrade enemy intelligence effectiveness in Close Area.** Forward presence forces and partners target enemy intelligence capabilities to complicate the enemy's collection plan and force the reallocation of assets at multiple levels. The division and the brigades degrade enemy tactical ISR through a combination of air defense against manned and unmanned aerial ISR, camouflage, and decoys. Tactical deception plans complicate the enemy's intelligence collection and may force the enemy to adjust their ground attack. The theater army coordinates with the division and the brigades for active anti-space ISR measures to support maneuver forces at critical times and spaces. The degradation and reallocation of the enemy's ISR capabilities in the Close Area cause the enemy to divert ISR resources from targeting friendly forces in the Support Areas, thereby enabling strategic and operational maneuver.

(3) **Deny enemy objectives.** Forward presence maneuver forces and partner nation conventional forces use the advantages of the defense, particularly in dense urban terrain, to attrit and slow enemy forces and enable the arrival of friendly expeditionary forces. Army forces leverage their preparation during competition to harden friendly urban areas to slow enemy advances and complicate its maneuver. The division and brigades employ organic cross-domain maneuver (primarily fires and air defense, as well as EW and aviation if a division is present) in conjunction with joint and Army multi-domain capabilities from the Support Areas (see next section) despite degraded communications. The field army assists the division and the brigades by shaping the fight in the Close Area through the accomplishment of three enabling tasks.

(a) **Converge joint fires from Support Areas and national-level capabilities.** The field army (or corps) supports the division and brigades in the Close Area by contesting enemy maneuver forces with long-range fires and coordinating for joint multi-domain capabilities. The field army (or corps) identifies high-priority targets (IADS, SRBM, long-range MRL, and command and control) in the Close Area and either strikes the target or disseminates the information to the division or brigades for their own targeting. Theater and operational fires commands, employing long-range fires, are initially the primary means of striking high-priority targets within the Close Area from the Support Area. Attacking these high-priority targets

requires resilience in multi-domain command and control at each echelon, provided through redundant means of communications, flexible command relationships, and multi-domain control measures designed to withstand degraded communications. The field army (or corps) balances the enduring requirement to neutralize the enemy's long-range fires with providing direct support to the division and brigades defending and executing maneuver in the Close Area.

(b) **Employ deception in the Close Area.** The field army uses deception plans developed in competition to create tactical unpredictability for the enemy and prevent the full massing of enemy lethal and nonlethal effects in the Close Area. The deception plans also present the enemy with mixtures of real, exaggerated, and false capabilities, especially in cyberspace and the EMS. Divisions and brigades execute deception in the Close Area by having multiple options to defend so even if the enemy gains access to U.S or partner planning, it must disperse reconnaissance assets among multiple possible locations of units, logistics, and multi-domain command and control nodes.

(c) **Contest the information environment.** The Joint Force, through the field army, immediately contests the information environment through the execution of IEO contingency plans with a credible, compelling message to bolster friendly political will and deny enemy information warfare objectives. These plans include prepared messages and methods of delivery based on anticipated wartime conditions, such as disruptions to civilian media and energy networks. Commanders in the Close Area exploit opportunities to take the initiative with images and messaging regarding friendly successes, particularly contesting the enemy advance and the rapid arrival of expeditionary forces, and disseminates it to the field army to shape public perception and reinforce the Joint Force Commander's campaign in the information environment.

e. **Maneuver across strategic and operational distances.** Executing maneuver across strategic and operational distances builds friendly combat power and sets the conditions for the dis-integration of the enemy's anti-access and area denial systems and the exploitation of the resulting freedom of maneuver. Army expeditionary forces use joint strategic transportation and prepositioned equipment to enter the theater at multiple points within days or weeks of the enemy's attack. Joint forcible entry operations can be employed to open additional lines of operations or initial entry points to enable these actions. Forward presence forces and national assets degrade enemy long-range surveillance and reconnaissance to reduce the enemy's effectiveness in attacking the lines of communications. In the area of operations, the theater and field army mitigate the effects of the enemy's attack throughout the Support Areas by executing deception plans to further complicate the enemy's ISR collection, protecting and hardening Army prepositioned stocks (APS), and conducting deployment and sustainment in dispersed formations along multiple routes.

(1) **Degrade enemy long-range ISR.** The theater and field armies have the responsibility to degrade the enemy's long-range ISR systems targeting the Operational and Tactical Support Areas. In both areas, friendly forces defeat or degrade enemy long-range reconnaissance across all domains, the EMS, and the information environment.

(a) **Counter enemy SOF and human intelligence (HUMINT).** Host nation counterintelligence, military, and internal security forces provide the primary means for countering enemy SOF and HUMINT networks in the Support Areas. The theater and field armies' counterintelligence and HUMINT assets collaborate with the host nation to generate a threat intelligence assessment and provide intelligence and enablers such as aviation, signals intelligence, EW, and cyberspace assets, to enable host nation's efforts. Security force assistance brigades, SOF, and civil affairs units also contribute to the strong relationships required to counter enemy SOF and HUMINT.

(b) **Counter enemy space ISR.** Prompt action by the theater army deprives the enemy of its primary means of long-range surveillance and significantly increases friendly survivability in the Operational Support Area. During the transition to armed conflict, the theater army provides offensive space and counter-space control for all ground forces in theater through either its organic capabilities or through coordination for joint capabilities. Although the theater army is the coordinating echelon, subordinate units down to brigade-level have responsibility to identify points in time and space that require the employment of necessary space capabilities to protect critical assets or movements. Proactively countering enemy space surveillance is particularly important in the Operational Support Area because the large number of potential targets spread across a wide geographic area that exceeds the capacity of enemy strategic reconnaissance and HUMINT. Effectively countering the enemy's space ISR capabilities causes the enemy to either accept more risk with strategic reconnaissance forces or shift to commercial space surveillance. Both of these actions create exploitable vulnerabilities.

(c) **Counter enemy cyber ISR.** The theater and field armies direct cyberspace defensive teams to protect critical systems for sustaining and deploying forces in the Support Areas. This requires detailed knowledge of the theater's networks, particularly its transportation and sustainment functions that have links to partner commercial, civilian, governmental, military, and coalition systems. Army forces counter the enemy's cyber reconnaissance and attacks with deception and traps, creating confusion and multiple presentations of false friendly systems to probing enemy cyber teams.

(2) **Mitigate effects of enemy attacks in the Support Areas.** The theater and field armies mitigate the effects of enemy attacks in the Support Areas to enable the reception of expeditionary forces executing strategic and operational maneuver. Multi-domain forces in the Support Areas employ deception to cause the enemy to expend resources on decoys or targets that have moved; miss fleeting opportunities; or expend high-value capabilities on less important targets. APS are protected and hardened to allow the rapid integration of expeditionary forces and the generation of combat power. Army forces in the Support Areas build resilience and redundancy by dispersing critical deployment and sustainment capabilities in mixed clusters and gain residual protection from air and missile defense radars and launchers, aerial surveillance, and other specialized protection capabilities that they would otherwise not be allocated.

(a) **Employ deception in Operational and Tactical Support Areas.** The theater and field armies conduct deception to complicate enemy ISR in their respective areas. Similar to deception in the Close Area, deception plans for the Support Areas employ multiples means to disperse enemy surveillance and reconnaissance and present a mixture of real, false, and

exaggerated capabilities to increase operational unpredictability. The friendly forces' deception plan must be coherent across all domains, the EMS, and the information environment to effectively counter the enemy's multi-domain reconnaissance.

(b) **Protect and harden Army prepositioned stocks (APS).** APS sites are a critical component of calibrated force posture. Hardened APS sites provide protection, especially against cruise missile attacks. The main defense for APS sites, however, is the ability to issue the equipment or supplies to expeditionary forces quickly, which requires maintaining stored equipment at high readiness levels, rehearsing rapid fielding procedures with designated expeditionary forces, and stockpiling of critical supplies and munitions to enable immediate employment in large-scale ground combat operations.

(c) **Disperse deployment and sustainment.** The theater army executes deployment and sustainment along multiple, dispersed routes. Army expeditionary forces deploy from the homeland and other regions using joint strategic transportation and arrive at multiple points in theater, proceed forward along multiple routes, and then occupy dispersed tactical assembly areas within range of enemy anti-access and area denial systems. Aviation units employ split basing between the Tactical and Operational Support Areas, or in the case of division formations, between the Tactical Support and Close Areas. Aircraft and units rotate through a network of dispersed, austere locations in the Tactical Support and Close Areas. Sustainment draws on multiple sources for local procurement and prepositioned supplies, distributed through dispersed supply nodes operated by forward presence units. Intensive sustainment-level maintenance of aviation, ground and electronic combat systems, including battle damage assessment and repair is conducted within the Operational Support Area's lower threat environment. The Army postures redundant sustainment infrastructure forward, plans and prepares precision logistics support, and ensures the availability of additional expeditionary capacity through proper balance across the Active and Reserve Components.

f. **Conclusion: Penetrate.** The Joint Force penetrates strategic and operational stand-off by immediately neutralizing the enemy's long-range systems, contesting enemy maneuver forces in all domains, the EMS, and the information environment, and conducting strategic and operational maneuver. The key to penetration is the neutralization of the enemy's long-range systems in decisive spaces enabled by Army long-range fires. The neutralization of these systems creates conditions for friendly forces to contest the enemy attack in the Close Area and for expeditionary forces to conduct strategic maneuver into theater. This initial penetration denies enemy objectives, builds friendly combat power, and enables the corps to begin the dis-integration of the enemy's long-range systems (high-tier IADS, SRBMs, long-range MRLs) and mid-range systems (mid-tier IADS, standard MRLs, self-propelled artillery) in decisive spaces.

3-7. MDO in armed conflict: Dis-integrate the enemy's anti-access and area denial systems

a. Multi-domain problem #3: How does the Joint Force dis-integrate enemy anti-access and area denial systems in the Deep Areas to enable operational and tactical maneuver?

b. Dis-integration of enemy anti-access and area denial systems requires the defeat of the enemy's long-range systems, the neutralization of the enemy's mid-range systems, and conducting operational maneuver to begin the dis-integration of the enemy's mid-range systems. These actions do not constitute a discrete phase, but overlap with the execution of penetration (described in the previous section, 3-6) and exploitation (described in section 3-8). Essential to the dis-integration effort is continuous refinement of intelligence through multiple domains to enable the Joint Force to see or stimulate and strike the enemy's remaining anti-access and area denial systems. This intelligence enables the field army's defeat of enemy long-range systems, building on the neutralization that began in penetration. It also allows the corps to begin the initial neutralization of the mid-range systems (MRL and cannon artillery) to enable operational maneuver of friendly ground forces. Operational maneuver completes the dis-integration by stimulating the remaining enemy mid-range fires and fixing and isolating enemy maneuver formations, generating favorable force ratios for friendly maneuver forces. The resulting dis-integration places maneuver forces in position to conduct rapid exploitation at decisive spaces and defeat the enemy.

c. **Refine intelligence of enemy anti-access and area denial systems.** Army forces provide the foundation of intelligence collection and analysis in the Close and Deep Maneuver Areas. The field army and corps continue to use the layered ISR network consisting of unmanned sensors, special operations forces, human intelligence, and high-altitude surveillance. Friendly intelligence collection focuses initially on locating the several dozen long-range systems of each combined arms army that prevent friendly air and ground maneuver forces from closing with the enemy (mid-tier IADS, SRBM, and long-range MRL). As dis-integration operations continue, the focus shifts to identifying the most critical and vulnerable elements of the enemy's mid-range systems. The enemy protects its critical systems with camouflage, concealment, and deception, so the field army and corps must converge multiple types of sensors to acquire targetable intelligence. The key to converging capabilities across all domains, the EMS, and the information environment is high-volume analytical capability and sensor-to-shooter links enabled by artificial intelligence, which complicates enemy deception and obscuration through automatic cross-cueing and target recognition. The intelligence refinement required for dis-integration depends on five interrelated systems.

(1) **Wide area surveillance.** The field army and corps require persistent, wide-area surveillance throughout the depth of the battlefield that is responsive to operational and tactical intelligence demands. The enemy will attempt to degrade this capability through both active (jammers, dazzlers) and passive (decoys, camouflage) means. Persistent, wide-area surveillance, therefore, requires redundancy with a mixture of space-based and high-altitude systems to complicate enemy countermeasures. The field army and corps are the primary echelons for employing persistent, wide-area surveillance because they have the analytical capability and capacity, communications and data infrastructure, and authorities to process, exploit, and disseminate high-volume data.

(2) **Penetrating reconnaissance.** Fifth-generation fighters and other penetrating joint air reconnaissance provide responsive collection of targets cued by persistent, wide-area surveillance, which requires resilient communications with these aircraft and ground terminals to access the information for the field army and the corps.

(3) **Stand-off surveillance and reconnaissance.** Joint and Army stand-off air surveillance and reconnaissance supplements the collection effort by focusing on signatures that identify high-priority enemy systems, particularly electronic intelligence for IADS, and rapidly processing and disseminating (within minutes) this intelligence to attack fleeting targets.

(4) **Expendable surveillance and reconnaissance.** Joint and Army expendable surveillance and reconnaissance (low-cost UAS, artillery- and air-delivered unmanned sensors) refine target locations cued by other forms of intelligence and also provide a means to stimulate enemy air defenses to allow collection by another sensor.

(5) **Human networks.** Special operations forces and their human intelligence networks provide intelligence about high-priority targets and disseminate this intelligence through non-standard communications systems to SOF coordination teams at the field army and corps.

d. **Defeat enemy long-range fires systems.** Army long-range fires formations in the field army's theater fires command, reinforced by the corps' operational fires command as required, converge with other joint capabilities to destroy or suppress enemy long-range systems (SRBM, mid-tier IADS, anti-ship missiles, and long-range MRL). The field army, when given responsibility for multi-domain command and control against enemy long-range systems, converges both joint and Army capabilities into multiple see-strike or stimulate-see-strike combinations against enemy systems that target friendly air and ground forces. The more combinations of see-strike options the Joint Force presents, the more likely the enemy will conclude that it is impossible to counter or mitigate them all and slows its rate of fire to preserve its critical systems. This makes stimulating and seeing enemy systems more difficult, but achieves the larger effect of creating freedom of maneuver for the Joint Force. By causing the enemy to shift to a passive, cautious posture, friendly forces gain the operational initiative and begin the dis-integration of the enemy's anti-access and area denial systems.

(1) **Stimulate long-range fires systems.** Stimulating enemy long-range systems (e.g., IADS radars) makes them visible for detection and destruction under tactical conditions favorable to the U.S. and partner forces. Army forces stimulate through deception or offensive action. Stimulation through deception employs decoys mimicking the signature of friendly aircraft, vehicles, or command nodes. Stimulation through offensive action uses cyberspace attacks in conjunction with maneuver and air, naval, or ground fires. Although many of the capabilities that stimulate enemy long-range systems are joint, the corps must possess the ability and authority to employ them when it commands and controls operations against enemy long-range systems.

(2) **See long-range fires systems.** The primary method for identification of enemy long-range systems is wide-area, persistent space-based or high-altitude surveillance rapidly disseminating data to a field army or corps analysis cell employing artificial intelligence or other computer assistive technologies to analyze the high volume of data. This combination allows identification of high-priority targets on a "cluttered battlefield" filled with thousands of signatures from military and civilian sources and complicated by enemy attempts at camouflage, concealment, and deception. The alternate method of "seeing" is with fifth-generation fighters, cyber capabilities, SOF and HUMINT teams, or artillery- or air-delivered UAS sensors tipped to

a location identified by another intelligence source that provided a reliable but low-fidelity location. Seeing enemy long-range systems in conjunction with stimulation requires a sensor tailored to the target and its expected reaction. For example, a counterbattery radar or a high-altitude ISR balloon with infrared sensors senses enemy long-range MRLs firing at a decoy friendly command post. Regardless of the sensor type, converging stimulation and sensing requires rapid analysis and dissemination (within minutes) because the enemy reaction offers only a brief window of superiority to exploit.

(3) **Strike long-range fires systems.** The Joint Force generates cross-domain synergy to overcome point defenses protecting enemy long-range systems. The main Army strike capability against enemy long-range systems is long-range precision fires (LRPF). It is the lowest cost, lowest risk, and most responsive method to attack enemy targets as they are identified in the Deep Maneuver and Deep Fires Areas. LRPF does not require suppression of enemy defenses for access, can be ready to fire in case the precise time of engagement is unknown, and can engage opportunity targets over large areas. LRPF, however, is best suited for attacking stationary targets due to its long time of flight. Naval strikes and stand-off air strikes (air-launched cruise missiles and similar systems) have characteristics similar to LRPF. Fifth-generation aircraft are the primary means of engaging moving targets or those with reliable but low-fidelity location data that the aircraft and pilot can improve. The Army's persistent enabling of the Joint Force to stimulate, see, and strike the enemy's long-range systems results in the initial key task in dis-integrating the anti-access and area denial systems.

e. **Neutralize enemy mid-range fires systems.** While the field army suppresses or defeats enemy long-range systems, the corps focuses on destroying enemy mid-range fires systems (self-propelled artillery and standard MRLs).[37] This effort occurs simultaneously with the operational maneuver (next section), with the corps shifting resources between the two as necessary. The corps' operational fires command destroys enemy mid-range fires by converging multiple see-strike combinations of Army and joint capabilities. While the enemy has dozens of long-range systems in each combined arms army, they possess hundreds of mid-range systems. In comparison to the long-range systems, attacking the large quantity of mid-range systems requires simpler methods of convergence that can be executed more quickly and on a larger scale. Rather than stimulate individual enemy radars, batteries, or battalions through meticulously planned stimulate-see-strike combinations (as required for the long-range systems), the corps creates simpler, quickly repeatable see-strike combinations to neutralize the enemy's mid-range systems. Presented with this approach, the enemy mid-range fires formations face a three-fold dilemma: support their at-risk maneuver forces and risk destruction by U.S. fires; displace and risk detection and destruction; or remain inactive, thereby leaving their maneuver forces without support and risk eventually being outmaneuvered or isolated.

(1) **See mid-range fires systems.** The corps employs multiple sensors to see enemy mid-range systems, which cover a large area over the duration of the counterfire fight (several days). During such an extended period, the enemy will counter any single surveillance or reconnaissance method, so the corps must present a shifting array of multiple, layered sensors to complicate enemy counteractions. The corps' primary system for identifying enemy mid-range fires systems before they engage is persistent, wide-area high-altitude or space-based

[37] With the division fires command, the division also has the capability to conduct a counterfire fight against enemy mid-range systems.

surveillance. The primary systems for identifying enemy fires as they engage friendly forces are counterbattery radars. Ground reconnaissance, unmanned and manned aerial systems, EW and signals intelligence units, SOF, space, and cyberspace reconnaissance forces augment these primary systems. In contrast with enemy long-range systems, which require the capacity to process a high-volume of data to find well-hidden but largely stationary targets, detecting mid-range fires systems is easier—a battalion volley of MRL creates a large signature—but requires fast processing and decision to strike the target before it displaces.

(2) **Strike mid-range fires systems.** The corps converges joint and Army capabilities against enemy mid-range fires systems. Destroying a large number of mobile systems requires simple, rapid forms of convergence, achieved by linking sensors directly to specific forms of strike. Air ISR cues air strike or ground fires; counterbattery radars and persistent, wide-area high-altitude surveillance cue ground fires; unmanned UAS cues attack aviation and ground fires. The ability of the corps to employ relatively simple air, space, and ground capabilities in layered combinations imposes greater complexity on enemy command and control systems without adding significant complexity to friendly actions. As friendly maneuver forces close within range of the mid-range systems, the division's fires will contribute to these strike efforts, especially against enemy mid-range systems able to effect march objectives and decisive spaces.

f. **Conduct operational maneuver.** Operational maneuver completes the dis-integration of the enemy's anti-access and area denial systems. The field army continues its defeat of the long-range systems, but transitions some capabilities to identifying high-value targets in the Close Area and either strikes them or rapidly disseminates the data to the corps to support their maneuver. The corps continues with its neutralization of mid-range systems and directs the division and brigades as they transit the Support Areas to the Close Area. The enemy will attempt to isolate and deny friendly maneuver forces support from adjacent units, multi-domain enablers, or higher echelons. Friendly maneuver forces, anticipating the implications of operating in such a contested environment, prepare to execute independent maneuver and practice intent-based synergy.

(1) Operational maneuver ideally occurs following the defeat of the enemy's long-range systems and the neutralization of the enemy's mid-range systems. To protect these critical systems, however, the enemy may employ them in a passive, but opportunistic posture capable of engaging friendly maneuver forces at critical places in either time or space. The corps and division, therefore, may have to maneuver forces in the Close Area and threaten to seize key terrain or isolate enemy maneuver forces to stimulate the enemy's mid-range systems.

(2) The corps and the division in the Close Area employ operational deception to fix enemy maneuver forces (a combined arms army or equivalent) and critical capabilities of their mid-range systems. The corps and division employ physical and virtual deception to generate uncertainty in the enemy's decision making, leaving forces or capabilities out of position or at a force ratio disadvantage relative to attacking friendly forces. Deception also prevents the enemy from gaining the full disposition of the friendly force and delays their recognition of decisive spaces. The corps also employs deception to stimulate the enemy mid-range system and enable its strike by multi-domain capabilities.

g. **Conclusion: Dis-integrate.** Operational maneuver, successfully executed, capitalizes on the neutralization of the enemy's mid-range systems to complete the dis-integration of the enemy's anti-access and area denial systems in decisive spaces. It also sets conditions for tactical success in the Close and Deep Maneuver Area by bringing sufficient combat power with momentum to bear in decisive spaces, ready to exploit opportunities. The dis-integration of the enemy's anti-access and area denial systems, however, is not a permanent condition. If given time, the enemy will regenerate the system through tactical adaptation, reorganization, and limited reconstitution. Because it is impossible to completely dis-integrate the entire anti-access and area denial capability of a near-peer enemy, commanders must exploit and enlarge windows of superiority to simultaneously complete the dis-integration of the enemy and further the exploitation of the resulting freedom of maneuver.

3-8. MDO in armed conflict: Exploit freedom of maneuver to defeat enemy objectives

a. Multi-domain problem #4: How does the Joint Force exploit freedom of maneuver to achieve strategic and operational objectives through the defeat of the enemy in the Close and Deep Maneuver Areas?

b. The Joint Force exploits the freedom of maneuver generated by dis-integrating the enemy's anti-access and area denial systems to defeat the enemy's mid-range systems, neutralize its short-range systems, and isolate and defeat enemy land forces through maneuver. Exploitation and maneuver sustains the penetration and dis-integration of the enemy's systems and enables the achievement of strategic objectives. The conditions for exploitation are achieved through MDO focused at decisive spaces. Army forces optimize the employment of multi-domain capabilities at decisive spaces and maneuver to dislocate the enemy's defense by physically, cognitively, and virtually isolating its subordinate elements, allowing friendly forces to achieve favorable force ratios and decisive tactical results. The physical, political, economic, social, and cultural importance of cities will often make them decisive spaces, critical to either denying enemy objectives or achieving friendly ones. The Joint Force, in dense urban terrain as well as all other terrain, links successful actions at decisive spaces to disrupt the enemy's operational plans, deny the enemy's strategic objectives, and, ultimately, achieve sufficient military superiority to attain friendly strategic objectives.

c. **Defeat the enemy's mid-range systems.** The corps continues to attack the enemy's mid-range fires during exploitation. The capabilities employed to see and strike are the same as those used to achieve the initial neutralization (see paragraph 3-7.e). The initial friendly success, however, will cause the enemy to attempt to preserve these systems by limiting their use and devoting greater effort to protection and survivability (e.g., more frequent survivability movements, greater dispersion). The combination of corps fires and division maneuver overcomes this enemy attempt to prevent the defeat of its mid-range systems, which are the most dangerous element of its tactical systems. Divisional maneuver compels the enemy to employ its remaining mid-range systems, which the corps' fires is ready to defeat. As the exploitation continues, the dislocation of the enemy defense caused by friendly maneuver offers increased opportunities to attack and overrun the enemy's fire and sustainment formations, completing the defeat of the enemy's mid-range systems at the decisive spaces.

d. **Neutralize the enemy's short-range systems.** The division converges a combination of capabilities across all domains, the EMS, and the information environment (e.g., attack aviation; UAS; short-range air defenses; EW; counter-position, navigation, and timing; cyberspace measures; fires; and maneuver forces) to neutralize the enemy's short-range systems. The division coordinates with the theater army for space control and space-based capabilities. The division coordinates with the field army (or corps if acting as Land Component Command) to integrate the division's organic air defense and aviation capabilities (to include UAS) with the joint air campaign. Although every echelon defends its own cyberspace, the senior tactical headquarters (field army or corps) allocates additional cyber defense teams to the division to neutralize the attacks that occur uniquely at short range. As the primary echelon responsible for managing the EMS, the division reinforces subordinate brigades with ground- and air-based EW capabilities, prioritizing support to air maneuver. The division supports the aviation brigade with both EW and fire support to suppress enemy air defenses and enable exploitation of tactical opportunities. The enemy has a significant number of short-range systems, which makes their neutralization essential to enabling maneuver.

e. **Maneuver to isolate and defeat land forces.** Divisions exploit freedom of maneuver by accessing joint multi-domain capabilities and employing their brigades at decisive spaces. The corps will play a significant role in supporting maneuver in dense urban terrain due to the increased need for converging joint and interagency capabilities. Ground forces that tactically overmatch the enemy are the foundation of the Joint Force's ability to exploit freedom of maneuver. Tactical overmatch is the product of adaptable, aggressive leaders and Soldiers organized in cohesive, well-trained formations; and aircraft, fighting vehicles, small units, and individuals with superior mobility, protection, and lethality. Divisions exploit the advantage of formation-level tactical overmatch by employing deception and maneuver to create favorable force ratios at decisive spaces. Divisions converge the abilities to see, deceive, and maneuver with multi-domain attacks against enemy communications, fires, and reserves. This convergence leads to breaking the physical, virtual, and cognitive cohesion of enemy formations, causing their defeat.

(1) **See.** Divisions and brigades employ their manned and unmanned air ISR, ground reconnaissance, and EW capabilities to see. These organic capabilities are supplemented by the corps, which analyzes data from high-volume sensors (e.g., space-based and high-altitude ISR) for subordinate echelons and translates that information to resilient low-volume data formats. This enables lower echelon units to access these intelligence sources even though they lack the analytical capability or communications links to exploit the sensors directly. The combination of organic reconnaissance and access to joint and national surveillance and intelligence provides commanders with additional options for sensing the enemy, which aids protection, deception, isolation, and maneuver.

(2) **Maneuver to isolate.** Divisions have primary responsibility for isolating enemy elements physically, virtually, and cognitively by converging air and ground maneuver, fires, EW, and deception. Additionally, divisions incorporate offensive space and cyberspace into this isolation of enemy elements by accessing these capabilities through the theater and field armies. The division fires command, combat aviation brigade, and coordinated air interdiction directed against enemy lines of communications, reserves, and adjacent units physically isolate maneuver

elements through fire. Division terrestrial and aerial EW capabilities coordinated with offensive space and cyberspace capabilities virtually isolate the enemy by disrupting enemy command and control systems with a particular emphasis on reconnaissance and fires. Friendly forces achieve both physical and virtual isolation through a combination of maneuver, the skillful use of terrain, exploiting the initiative, and deception to fix enemy reserves and adjacent units. The combination of physical, virtual, and cognitive isolation creates favorable force ratios for maneuver to exploit.

(3) **Maneuver to defeat.** The division is the foundational maneuver echelon. Divisions direct their brigades and Brigade Combat Teams to execute basic multi-domain convergence of maneuver, fires, EMS operations, and air support. Divisions employ brigades simultaneously to overwhelm the enemy through cross-domain fires and independent maneuver or in sequence to extend the duration of offensive operations. They can accomplish this even when isolated from higher headquarters for periods of time because of their organic fires, ISR, and ability to communicate locally with aircraft. Brigades integrate EW, medium-scale air operations, cyber attacks, and offensive space control into their maneuver. Independent brigades have the capability to conduct offensive operations for 72 to96 hours. Divisions and their brigades exploit tactical opportunities operating within the commander's intent to achieve decisive tactical results.

(4) **Maneuver in dense urban terrain.** Dense urban terrain poses a particular challenge to friendly exploitation of freedom of maneuver because it tends to slow the tempo of operations and consume significant quantities of supplies, enablers, and forces. In dense urban terrain, the division remains the foundational element of maneuver, but it will require additional support from the field army and corps to converge specialized capabilities and coordinate with multinational and interagency partners. If the commander decides to bypass dense urban terrain, then multi-domain capabilities can reduce the risk and cost of securing lines of communications through virtual isolation, use of unmanned sensors, and deception. In other instances, the Joint Force might enable coalition forces by augmenting them with multi-domain assets or capabilities. Army forces will fight in dense urban terrain when it is a decisive space due to its military, economic, or political value. Dense urban terrain offers increased possibilities for using cyberspace- and EMS-based weapons, but it also increases the requirements for using those capabilities precisely. Due to the potential for collateral damage to friendly forces or to civilian populations, the use of physical and virtual weapons will require detailed intelligence preparation, planning, and command oversight.

f. **Conclusion: Exploit.** The successful exploitation creates military conditions favorable to achieving strategic objectives. Rapid exploitation minimizes the strategic and operational cost to friendly forces and prevents the enemy from re-integrating its systems and consolidating gains in captured territory. In a conflict with a near-peer enemy armed with nuclear weapons, the operational exploitation, however, will conclude with some combination of policy, logistics, and resource constraints. Although the enemy's conventional forces will be severely degraded, it will retain cohesion and capabilities to remain a threat. If there is a period of extended political negotiation, the enemy will use the threat or limited resumption of conventional operations in conjunction with unconventional and information warfare to win diplomatic advantage and undermine the consolidation of gains by friendly forces. The Joint Force, therefore, might have

denied the enemy from achieving its objectives by penetration, dis-integration, and exploitation, but the full attainment of friendly strategic objectives requires a successful transition from conflict to return to competition.

3-9. MDO in return to competition: Re-compete to consolidate and expand gains

a. Multi-domain problem #5: How does the Joint Force re-compete to consolidate gains and produce sustainable outcomes, set conditions for long-term deterrence, and adapt to the new security environment?

b. The Joint Force and partners re-compete to retain and build upon the military advantages gained in conflict. In an operational environment where peer enemies have nuclear capacity, it is an unlikely expectation to hope for a vanquished opponent; some form of a return to competition and status quo is more realistic. The persistence and presence of ground forces allow the U.S. to consolidate gains and provide continuing deterrence until the adversary no longer seeks to overturn the outcome through a return to armed conflict. In the return to competition, Army forces conduct three concurrent tasks: physically secure terrain and populations to produce sustainable outcomes; set conditions for long-term deterrence by regenerating partner and Army capacity; and adapt force posture to the new security environment.

c. **Produce sustainable outcomes.** In the return to competition, the field army retains overall command of Army conventional combat forces in their area of operations. The primary mission of these forces is to retain the physical and psychological advantages over the enemy achieved during armed conflict and secure key terrain and friendly populations. If the expeditionary corps redeploys, the field army resumes the role of converging large quantities of capabilities against the adversary's remaining mid-range fires. The potential for conventional lethal operations to take place, either in sporadic clashes during the return to competition or through the return to armed conflict, requires the field army to continue intelligence preparation of the battlefield. Actions in cyberspace, however, will likely continue at a high intensity level similar to that of the armed conflict, because physical separation of the armies will not ensure that either will surrender access to cyberspace. Operations in the information environment will also continue as both sides seek to consolidate gains by influencing friendly and enemy civilians, militaries, and governments. Civil affairs activities support partner governments to re-establish essential services and governance. At the same time, the theater army supports joint and multinational irregular warfare against other proxies outside of the field army's area of operations and supports any allied corps or division deterring enemy conventional attacks outside the field army's area of operations. Taken together, these Army efforts at echelon consolidate gains rapidly and create a foundation for deterrence.

d. **Set conditions for long-term deterrence.** Army forces set conditions for long-term deterrence by regenerating and expanding both Army and partner capacity. Forward presence Army forces use defensive planning and preparation that deter a return to conflict as a means of building greater interoperability with partner forces. The field army also uses the relative freedom of maneuver in all domains, the EMS, and the information environment afforded by the post-conflict environment to set the conditions for a sustainable, advantageous calibrated force posture. The Army enables deterrence by rapid regeneration of munitions stockpiles, which will be severely depleted after even a relatively short campaign. Army forces assist the building or

regenerating of partner capabilities and capacity for self-defense against conventional and unconventional threats. SOF and security force assistance forces are essential to rebuilding partner capacity and strengthening deterrence. From the adversary's perspective, the Joint Force's and Army's actions show an increasing and enduring ability to counter aggression, demonstrated through robust exercises, cyber reconnaissance, and information operations. In combination, they renew and set conditions for long-term deterrence.

e. **Adapt to the new security environment.** Conflict causes significant changes to regional security environments. Army forces provide persistent presence to ensure the new security environment is advantageous for the U.S. and its partners. The theater and field armies coordinate with partners, joint headquarters, and Headquarters, Department of the Army to best adapt calibrated force posture to the new operational environment. Army forces retain the capability to immediately counter and rapidly renew offensive operations. Reserve component formations extend Army presence while allowing the regeneration of expeditionary readiness.

f. **Return to competition.** Through a successful transition from armed conflict to the return to competition, the Joint Force translates operational success in armed conflict to the attainment of strategic objectives. The consolidation of gains, reconstitution of friendly forces, and building capacity of partners enables long-term deterrence of renewed armed conflict. More importantly, the successful adaptation to the new security environment results in an overall improvement of the United States' strategic position.

Chapter 4
Conclusion

a. The *U.S. Army in Multi-Domain Operations* concept challenges Army leaders to visualize and conduct maneuver in fundamentally new ways that enable the defeat of Chinese and Russian systems. Convergence enables Army forces to compete with capable adversaries, and to penetrate and dis-integrate their anti-access and area denial systems—even when out-numbered—by attacking vulnerabilities in the enemy's military system. Convergence, however, will not be easy to achieve. Army headquarters must not only have the technical, intellectual, and doctrinal tools to execute multi-domain command and control, but rigorous joint and combined training to realize it. In this way, Army forces achieve intent-based synergy across all domains, the EMS, and the information environment to compete, penetrate, dis-integrate, exploit, and re-compete.

b. The Army organizes for MDO with echeloned formations that conduct intelligence, maneuver, and strike activities across all domains, the EMS, and the information environment.[38] Army formations maneuver by moving and linking capabilities in multiple or unexpected ways and sequences to defeat or destroy adversaries' military systems. This method of maneuver at echelon by Army forces overwhelms Chinese and Russian military systems at critical spaces

[38] The *U.S. Army Functional Concept for Movement and Maneuver, 2020-2040* defines cross-domain maneuver as "the employment of mutually supporting lethal and nonlethal capabilities in multiple domains to generate overmatch, present multiple dilemmas to the enemy, and enable Joint Force freedom of movement and action."

with multiple dilemmas and massed effects, creating windows of superiority for the Joint Force to accomplish objectives.[39]

c. MDO requires the Army to develop or improve capabilities to contribute cross-domain options to the Joint Force, by:

(1) Calibrating force posture geographically and across all the Army components to defeat Chinese and Russian offensive operations in competition and to deter escalation to armed conflict.[40]

(2) Preparing the operational environment by building partner capacity and interoperability and setting the theater through such activities as establishing basing and access rights, prepositioning equipment and supplies, conducting preparatory intelligence activities, and mapping EMS and computer networks.[41] (Supported by Army Materiel Modernization Priorities: Army Network)

(3) Building partners' and allies' capacities and capabilities to defeat increasingly sophisticated Chinese and Russian -sponsored unconventional and information warfare.

(4) Preparing the operational environment for competition and conflict by building understanding of and capabilities in select urban areas of particular operational or strategic importance.

(5) Establishing precision logistics that provides a reliable, agile, and responsive sustainment capability necessary to support rapid power projection, MDO, and independent maneuver from the Strategic Support Area to the Deep Maneuver Area. (Supported by Army Materiel Modernization Priorities: Future Vertical Lift, Army Network)

(6) Establishing necessary authorities and permissions normally reserved for conflict or to higher echelons to operate in competition and rapidly transition to conflict effectively.

(7) Improving the capability to conduct MDO in dense urban terrain at all echelons through the development of tactics and capabilities to increase the accuracy, speed, and synchronization of lethal and nonlethal effects. (Supported by Army Materiel Modernization Priorities: Long Range Precision Fires, Next Generation Combat Vehicle, Army Network, Soldier Lethality)

(8) Supporting a credible U.S. information narrative through cross-domain actions that communicate and counter threats by Chinese and Russian reconnaissance, strike, combined arms, and unconventional warfare capabilities.

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[39] As an example, Army formations can maneuver—or assist Joint Force maneuver—as a reconnaissance action, fighting to gain intelligence, key terrain, and set conditions that enable strikes, rather than maneuvering only after passive intelligence collection, deliberate analysis, and precision strikes have prepared the battlefield for maneuver.
[40] The idea of calibrating and re-calibrating force posture globally aligns with the idea of "forming operationally coherent forces" as described in the Joint Concept for Rapid Aggregation.
[41] "Setting the theater" encompasses the actions to establish and maintain conditions to seize the initiative and retain freedom of action for a specific theater. These actions may occur outside of the theater, as well.

(9) Enabling commanders and staffs at each echelon to visualize and command a battle in all domains, the EMS, and the information environment and shift capabilities rapidly between domains and organizations to mass combat power against Chinese and Russian vulnerabilities. This requires new tools to more rapidly converge capabilities across the Joint Force, shifting training paradigms, and changing personnel and talent management practices. This also requires that Army formations be trained, manned, and equipped to leverage all available information, from national, joint, commercial, and Service repositories and libraries, or directly from collection assets seamlessly and in a time dominant manner. (Supported by Army Materiel Modernization Priorities: Army Network, Soldier Lethality)

(10) Providing to the Joint Force Commander multi-domain formations and systems that can converge capabilities to attack specific vulnerabilities in Chinese and Russian multi-layered, mutually reinforcing military forces and systems. This means creating commanders and staffs who have the means and ability to access and employ capabilities that reside across the Joint Force. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Soldier Lethality)

(11) Providing to the Joint Force Commander with multi-domain formations that have systems, leaders, and Soldiers that are durable, can operate in a highly contested operational environment, cannot easily be isolated from the rest of the Joint Force or from partners, and able to conduct independent maneuver and employ cross-domain fires. This requires extended sustainability of systems and formations, and leaders and Soldiers who continue to operate effectively in austere environments and conditions. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Army Network, Air and Missile Defense, Soldier Lethality)

(12) Consolidating gains through clear demonstrations of U.S. security commitments to partners through combined exercises, training, and other presence activities.

(13) Enabling and complementing land, air, and maritime capabilities with operations in space, cyberspace, and the EMS to support the opening of and exploitation of windows of superiority creating dilemmas for the enemy while protecting the ability to conduct friendly operations in degraded, disrupted, and/or denied operational environments.

(14) Attracting, retaining, and making maximum use of high-quality, physically fit, mentally tough Soldiers who have the skills and expertise to conduct MDO.

d. The *U.S. Army Multi-Domain Operations* concept drives experimentation; informs capability and doctrine development; and frames organizational trade-offs and force posture decisions that restore the Army's ability as part of the Joint Force to deter adversaries that utilize Chinese and Russian systems. MDO is at present an Army concept—informed by contributions from other Services and partners—describing Army contributions to and requirements for a joint campaign conducted alongside partners against near-peer adversaries. Future development of MDO will test the method of operations described in this edition of the concept in other scenarios and with even greater involvement from the Joint Force and partners.

Appendix A
Assumptions

A-1. Baseline Assumptions

a. The U.S. Army will remain a professional, all-volunteer force, relying on all components of the Army to meet future commitments.

b. The Army will adjust to fiscal constraints and have resources sufficient to preserve the balance of readiness, force structure, and modernization necessary to meet the demands of the national defense strategy in the mid- to far-term (2020 to 2040).

c. Except for an immediate response to a national emergency, the Army will conduct operations as part of joint, interagency, and multinational teams.

A-2. Fundamental assumptions

a. Adversaries will challenge U.S. interests by means and with ways below the threshold of armed conflict and short of what the U.S. considers war.

b. Adversaries can conduct armed conflict via regional campaigns with limited warning to seize limited strategic objectives and consolidate gains within days or weeks.

c. The proliferation of precision-guided weapons, integrated air defenses, cyberspace weapons, counterspace weapons, and other technologies allows an increasing number of potential adversaries to contest and hold at risk U.S. forces in all domains, the EMS, and the information environment at the tactical, operational, and strategic levels.

d. U.S. and partner political authorities will authorize and enable sufficient force posture and readiness levels to respond to and defeat near-peer adversaries if deterrence fails.

e. U.S. and partner governments will provide authorities for friendly forces to conduct operational preparation of the environment, as well as offensive EMS, cyberspace, space, unconventional warfare, and information environment operations to deter and defeat adversaries.

f. U.S. and partner government agencies, headquarters, and fielded forces will develop and sustain sufficient interoperability between Services, government agencies, and allies to conduct combined operations that deter and defeat adversaries.

g. Neither the U.S. nor adversaries will *employ* nuclear weapons. The use of such weapons would so significantly alter the strategic context that different operational approaches would be required. (This assumption does not mean that this concept ignores the *threat* of nuclear weapons. Army forces must be resilient against all possible forms of attack. Furthermore, commanders will have to account for the possibility of nuclear attack in formulating schemes of maneuver and accounting for the risk of escalation that might lead to operational restrictions on where and how the Joint Force operates.)

Appendix B
Key Required Capabilities

B-1. Introduction. This appendix lists capabilities needed to conduct MDO as described in this concept.

B-2. Required capabilities

a. To conduct MDO in a highly contested environment, Army forces require the ability to calibrate force posture geographically and across all the Army components to defeat Chinese and Russian offensive operations in competition and to deter escalation to armed conflict. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires)

b. To conduct MDO in a highly contested environment, Army forces require the ability to prepare the operational environment by building partner capacity and interoperability and setting the theater through such activities as establishing basing and access rights, prepositioning equipment and supplies, conducting preparatory intelligence activities, and mapping EMS and computer networks. (Supported by Army Materiel Modernization Priorities: Army Network)

c. To conduct MDO in a highly contested environment, Army forces require the ability to build partners' capacities and capabilities to defeat increasingly sophisticated Chinese and Russian -sponsored unconventional and information warfare.

d. To conduct MDO in a highly contested environment, Army forces require the ability to prepare the operational environment for competition and conflict by building understanding of and capabilities in select urban areas of particular operational or strategic importance.

e. To conduct MDO in a highly contested environment, Army forces require precision logistics that provides a layered, agile, and responsive sustainment capability necessary to support operations from the Strategic Support Area to the Deep Maneuver Area. Precision logistics is enabled by: a sustainment enterprise resource planning decision support system with predictive analysis tools and the ability to resupply without request and/or redirect supplies based on priority; a real-time common operating picture viewable by commanders and logisticians at echelon; and significant demand reduction across the Total Force to lessen delivery requirements by as much as 50% and extend operational time and reach of formations.

f. To conduct MDO in a highly contested environment, Army forces require necessary authorities and permissions to operate in competition and rapidly transition to conflict effectively.

g. To conduct MDO in a highly contested environment, Army forces require the ability to conduct MDO in dense urban terrains at all echelons with tactics and capabilities that increase the accuracy, speed, and synchronization of lethal and nonlethal effects. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicle, Army Network, Soldier Lethality)

h. To conduct MDO in a highly contested environment, Army forces require the ability to support a credible U.S. information narrative through cross-domain actions that communicate and counter threats by Chinese and Russian reconnaissance, strike, combined arms, and unconventional warfare capabilities.

i. To conduct MDO in a highly contested environment, Army forces require the ability to enable commanders and staffs at each echelon to visualize and command a battle in all domains, the EMS, and the information environment and shift capabilities rapidly between domains and organizations to mass combat power against Chinese and Russian vulnerabilities. This requires new tools to more rapidly converge capabilities across the Joint Force, shifting training paradigms, and changes in personnel and talent management practices. This also requires that Army formations be trained, manned, and equipped to leverage all available information, from national, joint, commercial, and Service repositories and libraries, or directly from collection assets seamlessly and in a time dominant manner. (Supported by Army Materiel Modernization Priorities: Army Network, Soldier Lethality)

j. To conduct MDO in a highly contested environment, Army forces require the ability to provide to the Joint Force Commander multi-domain formations and systems that can converge capabilities to attack specific vulnerabilities in Chinese and Russian multi-layered, mutually reinforcing military forces and systems. This means building tactical formations and leaders that can think through, access, and/or employ capabilities that reside across the Joint Force. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Soldier Lethality)

k. To conduct MDO in a highly contested environment, Army forces require resilient multi-domain formations with systems, leaders, and Soldiers that are durable, can persist in a difficult operational environment, cannot easily be isolated from the rest of the Joint Force or from partners, and able to conduct independent maneuver and employ cross-domain fires. This requires extended sustainability of systems and formations, and leaders and Soldiers who continue to operate effectively in austere environments and conditions. (Supported by Army Materiel Modernization Priorities: Long-Range Precision Fires, Next Generation Combat Vehicles, Future Vertical Lift, Army Network, Air and Missile Defense, Soldier Lethality)

l. To conduct MDO in a highly contested environment, Army forces require the ability to consolidate gains through clear demonstrations of U.S. security commitments to partners through combined exercises, training, and other presence activities.

m. To conduct MDO in a highly contested environment, Army forces require the ability to enable and complement land, air, and maritime capabilities with operations in space, cyberspace, and the EMS to support the opening of and exploitation of windows of superiority, creating dilemmas for the enemy while protecting the ability to conduct friendly operations in degraded, disrupted, and/or denied operational environments.

n. To conduct MDO in a highly contested environment, the Army must attract, retain, and make maximum use of high-quality, physically fit, mentally tough Soldiers who have the skills and expertise to conduct MDO.

Appendix C
MDO Supporting Ideas

C-1. Maneuver in MDO

a. Maneuver is the combination of movement and fires to achieve positions of advantage that defeats the enemy.[42] Movement is the adjustment of the physical location of a capability to another more favorable location. In addition to the physical effect of repositioning, movement usually produces cognitive effects on the enemy, as well. All military capabilities originate from a physical location and undergo movement (of some form) when employed, even those capabilities intended to produce cognitive or virtual effects. Fires are the destructive or disruptive effects a formation or asset produces on an enemy. Fires can produce a combination of physical, virtual, and cognitive effects on the enemy. Fires, even if they are particles or waves, must also travel through a domain to reach their intended target, which is also a physical location, even if the target is a computer or a human mind.

b. MDO requires fires and maneuver to operate within and across domains. Cross-domain fires and cross-domain maneuver exploit an opportunity from one or more domains intended to achieve an advantage in another domain.

(1) *Cross-domain maneuver* is the employment of mutually supporting lethal and nonlethal capabilities of multiple domains to create conditions designed to generate overmatch, present multiple dilemmas to the enemy, and enable Joint Force freedom of movement and action.

(2) *Cross-domain fires* is the integration and delivery of lethal and nonlethal fires across all five domains (land, maritime, air, space and cyberspace), the EMS, and the information environment.

c. Cross-domain maneuver and cross-domain fires are a realization that a commander must visualize and exploit the physical, virtual, and cognitive effects of maneuver and fires in multiple domains and environments over time. For example, a ground tactical formation must operate in (and potentially affect, if it contains appropriate cross-domain capabilities) the relevant air and maritime domains above or adjacent to its land-based area of operations, as well as understand cyberspace, EMS, information environment, and space activities that can impact friendly operations. Based on this visualization, the commander must converge organic and available Joint Force capabilities in time and at the proper place to identify, create, and exploit windows of superiority.

C-2. MDO framework

a. The operational environment, threats, and problems envisioned in MDO demand a framework that brings order to the complexities of a multi-domain environment. Because near-peer adversaries contest and can deny all domains, the EMS, and the information environment at extended distances, current and anticipated future problems exceed what could be assigned

[42] An enemy force is defeated when it has temporarily or permanently lost the physical means or the will to fight. To defeat the enemy, joint forces destroy, dislocate, dis-integrate, and isolate enemy forces.

within a single area of operations under the current joint operational framework. The MDO framework must also account for all domains, extending to space and cyberspace, as well as the EMS and information environment, because activities in these domains across time produce tactical, operational, and strategic effects not captured by the existing joint framework.[43] An expanded multi-domain framework allows commanders to arrange operations in the emerging operational environment. The MDO framework (see figure 2-1) provides an expanded physical framework from which to reference actions across all domains, the EMS, and the information environment conducted by the Joint Force, partners, adversaries, and enemies.

b. Since the MDO framework is operational, it is also grounded in physical spaces. Abstract aspects more evident in some domains are also grounded physically, despite their predominantly immaterial presentations. At some point, all the abstract elements (cognitive, virtual, informational, and human) demonstrate their effects physically at a place or in an area through a system or people. Representing these elements in a physically based framework clarifies an already very complex multi-domain operational environment for commanders and staffs. The following description of the framework places all friendly and enemy activities and physical locations in categories of physical space as the fundamental visualization layer.

c. The areas in the MDO framework are defined by the mixture of capabilities (both friendly and enemy) available for use within each area. MDO take a different form in each area because the two contending sides have a different mixture of capabilities available for competing and fighting. Because of the expanded battlefield in which actions in one area can influence another, the breadth of the battlefield needs to be placed within a single, simple framework to illustrate these sometimes complex relationships. Though depicted geometrically for simplicity, the areas within the framework are not defined by geographic space or relationships. In some theaters, for example, a Deep Maneuver Area could be physically adjacent to an Operational Support Area due to the types of capabilities available to each side. The complementary nature of unique and interoperable Service capabilities provides the Joint Force multiple options to maneuver in areas inaccessible to single-Service and single-domain solutions. Previous depictions of the battlefield did not capture the full range of places and times that friendly and enemy capabilities interact in the current and future operational environment. This increased number of battlefield areas, expansion in geographic area, and extended time horizons are new features of MDO.

d. **MDO framework spaces**

(1) **Deep Fires Areas**: The Operational and Strategic Deep Fires Areas comprise the Deep Fires Areas. These areas are defined as the areas beyond the feasible range of movement for conventional forces but where joint fires, SOF, information, and virtual capabilities can be employed. Operational and Strategic Deep Fires Areas are differentiated by the types of capabilities that can, or are authorized, to operate in each area. These areas are either too far (beyond operational reach) for conventional maneuver forces to enter or they are prohibited by policy (such as an international border).[44] Therefore, operations in the Deep Fires Areas are

[43] FM 3-0, C1 dated 6 Dec 2017 incorporates some of the ideas related to the framework proposed by this concept (pp. 1-29 to 1-35).
[44] In cases where policy restrictions create Deep Fires Areas, the areas might be geographically non-contiguous. For instance, in a counterinsurgency campaign the Joint Force might have full freedom of action within the host country but is allowed to use only virtual capabilities against the enemy sanctuary in a neighboring country. In that instance, the international border would represent the boundary between Close and Deep Fires Areas.

limited to whatever physical and virtual capabilities are permitted by law or policy and that can operate in the heart of enemy defenses. This limited accessibility and the inherent difficulty of operating deep within enemy territory place a premium on the ability to combine and employ whatever capabilities are available from across all domains, the EMS, and the information environment.

(2) **Deep Maneuver Area**: This area is the highly contested area where conventional maneuver (ground or maritime) is possible, but requires significant support from multi-domain capabilities; commanders must make a concerted effort to "break into" the Deep Maneuver Area. Because more friendly capabilities possess the range and survivability to influence or operate within this space than in the Deep Fires Areas, and because commanders can take advantage of the combination of fire and movement, there are many more options for Joint Force employment here than in the Deep Fires Areas. Moreover, the persistence of ground and maritime maneuver forces allows operations to persist for far longer than in the Deep Fires Areas, where effects will often be more transitory. In most anticipated campaign designs, many operational objectives are in the Deep Maneuver Area.

(3) **Close Area**: The Close Area is where friendly and enemy formations, forces, and systems are in imminent physical contact and will contest for control of physical space in support of campaign objectives. The Close Area includes land, maritime littorals, and the airspace over these areas. The new operational environment and improved enemy and friendly capabilities have expanded the Close Area. Operations in the Close Area require tempo and mobility in order to overcome these enemy capabilities through sufficiently integrated and concentrated combat power at the critical time and space. Characteristics of the Close Area present challenges to integrating cross-domain capabilities because of the reduced time available to access and employ enablers, such as centrally controlled, low-density capabilities. Commanders employ capabilities from all domains, the EMS, and the information environment, organic and external, in the Close Area to generate complementary effects of combined arms, but speed of action, coordination, and synchronization of effects place a premium on organic capabilities. Operations in the Close Area are designed to create windows of superiority for maneuver to defeat enemy forces, disrupt enemy capabilities, physically control spaces, and protect and influence populations.

(4) **Support Areas**: Collectively, the Support Areas represent that space in which the Joint Force seeks to retain maximum freedom of action, speed, and agility and to counter the enemy's multi-domain efforts to attack friendly forces, infrastructure, and populations. The nature of these threats varies with the adversary, though with current technology virtually all adversaries will have reach into the homeland (for example, through cyberspace, information warfare, agents, sympathizers, and space), even if only by using social media to undermine public support and encourage "lone-wolf attacks." The reach of regional powers is also growing and the most potent adversaries already possess multiple advanced cyberspace, space, and physical capabilities (air, naval, special operations, and/or missile forces) that can contest the friendly rear areas at all times. Though enemy capabilities will vary with the situation, a common requirement will be the need to ensure that responsibilities, resources, and authorities are properly aligned among echelons, functions, and political organizations. Consequently, the

Support Areas are divided according to friendly and enemy capabilities typically operating in each area.

(a) The Strategic Support Area: This area is the area of cross-Combatant Command coordination, strategic sea and air lines of communications, and the homeland. Most friendly nuclear, space and cyberspace capabilities, and important network infrastructure are controlled and located in the Strategic Support Area. Joint logistics and sustainment functions required to support MDO campaigning throughout competition and armed conflict emanate from the Strategic Support Area. The enemy will attack the Strategic Support Area to disrupt and degrade deployments and reinforcements attempting to gain access to the Operational Support Area and move to the Close Area, taking advantage of the reach of strategic lethal and nonlethal weapons, as well as special operations reconnaissance and strikes. Enemy engagements in the Strategic Support Area will drive a rapid tempo of friendly operations in other areas to seek decision and limit enemy options for escalation.

(b) The Operational Support Area: This is the area where many key Joint Force mission command, sustainment, and fires/strike capabilities are located; these can be land or sea-based. This area normally encompasses many entire nations, thus making the Operational Support Area an important space for friendly political-military integration. Due to the political and military importance of the Operational Support Area, the enemy targets this area with substantial reconnaissance, information warfare, and operational fires capabilities. Friendly units maneuvering in the Operational Support Area, therefore, are never out of contact. The Joint Force will enable friendly operations in this area by dedicating significant capacity during armed conflict to open windows of superiority in the Operational Support Area that enable friendly operations.

(c) The Tactical Support Area: This is the area that directly enables operations in the Close, Deep Maneuver, and Deep Fires Areas. Many friendly sustainment, fires, maneuver support, and mission command capabilities are in the Tactical Support Area. The enemy directs information warfare, unconventional warfare, tactical fires, maneuver forces, and even operational fires at friendly forces, populations, and civil authorities in the Tactical Support Area. Friendly units in the Tactical Support Area must be prepared to endure threat fires and defeat enemy ground force infiltration through and penetrations of the Close Area. Mobility and survivability are key requirements for friendly forces operating in or rapidly transiting this area.

C-3. MDO at echelon

a. **Theater army.**

(1) In competition and return to competition:

- Set conditions for competitive campaigning by working with joint and multinational partners to defeat information and unconventional warfare in countries away from the adversary’s near abroad

- Translate tactical successes in defeating information and unconventional warfare by using aggressive competition as a means to deepen cooperation and improve the U.S.'s strategic posture in the region

- Deter armed conflict by building resilience in friendly command and control, sustainment, and other force generation capabilities located in the Operational Support Area, with a particular focus on enabling quick draw of APS

- Coordinate with partners on cyberspace defense of key logistics and transportation systems; develop resilience by creating back-up methods to ensure sustainment

- Set the theater intelligence architecture, provide access to theater collection and databases, conduct open source intelligence in support of IEO, establish intelligence partnerships, facilitate intelligence engagement, and provide counterintelligence in support of force protection in the Operational Support Area

(2) In conflict:

- Counter enemy SOF actions against the Operational Support Area through the provision of intelligence and enablers to partner security forces

- In conjunction with other components, provide ballistic and cruise missile defense for critical targets

- Enable joint maneuver in the Close and Deep Areas through long-range fires provided by the Theater Fires Command

- Coordinate offensive space control for Army forces

b. **Field army.**

(1) In competition and return to competition:

- Set the campaign through focused tactical and technical intelligence on critical adversary military systems that then drives war and deployment plans, training, and resource decisions

- Set the campaign through creation of multi-layered ISR belts in likely areas of enemy aggression

- Coordinate with the Air Component to ensure continuity of support in the Close Area

- Set conditions for competitive campaigning by working with joint and multi-national partners to counter information and unconventional warfare in countries most threatened by the adversary

- Translate tactical successes in countering information and unconventional warfare by using aggressive competition as a means to deepen cooperation and improve the U.S.'s strategic posture in the region with most threatened partners

- Deter armed conflict by building resilience in the Tactical Support Area so that U.S. and partner forces can stage a credible force within range of adversary anti-access and area denial systems

- Orchestrate actions with information environment operations to counter adversary narratives in the most threatened partner countries

(2) In conflict:

- Counter enemy SOF actions against the Operational Support Area through the provision of intelligence and enablers to partner security forces

- Employ Army high-altitude ISR platforms to develop stand-off intelligence of enemy mid-range IADS and fires

- Coordinate complex joint convergence (air and naval strikes, cyberspace) in support of corps scheme of maneuver or on behalf of subordinate echelons

- Be prepared to assist theater army with enabling joint maneuver

c. **Corps.**

- Coordinate complex joint convergence if no field army present

- Employ divisions simultaneously to overwhelm enemy or in sequence to extend the duration of operations

- Provide access to subordinate echelons by tailoring high-volume intelligence requiring significant analysis capacity and communications bandwidth to manageable data

d. **Division.**

- Coordinate complex electromagnetic and information operations convergence

- Employ brigades simultaneously to overwhelm enemy or in sequence to extend the duration of operations

e. **Brigade.**

- Coordinate simple convergence of maneuver, ground, and air internally and be able to integrate complex convergence into scheme of maneuver with the assistance of higher echelons

- Conduct independent maneuver based on intent and employing internal convergence and resilience if physically and virtually isolated

C-4. Convergence considerations

a. Physical, virtual, and cognitive capabilities across the domains, environments, and functions often possess substantially different time characteristics that govern how they can be employed. When creating and exploiting windows of superiority, commanders must visualize and execute combined arms maneuver in new ways because the varied characteristics of different capabilities that must be converged at a place or places to achieve a purpose impose unique time considerations to operations. The Joint Force and its partners must also reconsider time in terms of converging actions during competition to achieve objectives without resort to, but also through transition to, armed conflict and a return to competition. To support converging capabilities in time and purpose at decisive spaces, MDO proposes five elements—preparation time, planning and execution time, duration time, reset time, and cycle time—to visualize the convergence of capabilities. Preparation time is the time required to produce conditions required for a capability's employment. Planning and execution time is the time required to initiate movement combined with the time required to move or transmit to the objective. Duration time is the time that a capability produces the intended effect. Reset time is the time required to regenerate a capability between employments. Cycle time is one iteration of planning through reset time. Understanding time is both art and science as elements of time for some capabilities, such as planning and execution time for a ballistic missile attack, can (or must) be known with great certainty while other aspects, such as duration of a cyberspace effect, can only be estimated.

b. At the operational level, MDO requires the modulation cycles and usage rates. There is an art and a science to the application of convergence. Perfect synchronization is generally unobtainable due to operational constraints. Additionally, utilizing all available assets at once may not support desired operational outcomes. Some assets have limited-use timeframes and must be held back for when the application has the highest payoff. Commanders will invariably accept less-than-perfect multi-domain synchronization in order to maintain a higher tempo. The mission dictates campaign tempo, not domain synchronization.

c. Figure C-1 provides general characteristics for the four cycles (ground, air, maritime, and enduring virtual weapons).

Cycle Type	Build-up Time (if not already present in theater)	Persistence When Employed	Reset Interval
Ground[45]	Very long (months)	Long (days)	Long (days to weeks)
Air	Short (days)	Short (hours)	Short (hours to days)
Maritime	Medium (weeks)	Very long (months)	Very long (weeks)[46]
Enduring virtual weapons (cyberspace/space/EW)	Short (days)[47]	Very short (seconds to minutes)	Very short (minutes to hours)[48]

Figure C-1. Characteristics of the ground, air, maritime, and enduring virtual weapons cycles

d. The two usage rates are preferred munitions and expendable virtual weapons. As opposed to the cycles representing capabilities that can be continually used so long as they do not suffer attrition, the two usage rate categories decrease with use. Due to the significant time required to replenish these stockpiles when compared to the anticipated usage, it is only a slight oversimplification to regard them as essentially a fixed arsenal that must be carefully managed. Losing the "battle of the burn rates" and thereby being forced to severely curtail the use of preferred munitions or expendable virtual weapons while the adversary still has significant quantities would put the Joint Force at a severe disadvantage. Put differently, failing to manage usage rates in conjunction with the four cycles nullifies MDO and effectively returns one side to the 20th century while their better-supplied (or more judicious) enemy retains 21st century capabilities.

e. In conjunction, the limits of the four cycles and two usage rates define the art of the possible at the operational level. The Joint Force Commander's allocation of resources and risks within each establishes the tempo of the campaign. There is no fixed relation among these cycles and usage rates; the proper balance will vary according to the situation. The essential takeaway is that the degree of multi-domain capability will vary over the course of a campaign. Tactical commanders should not assume that all domain capabilities will be available at any given time.

[45] For instance, the deployment of a division with some combination of Stryker and Armored Brigade Combat Teams would require several months, particularly against an adversary capable of contesting strategic lines of communications. In a deliberate offensive operation, the division might be able to sustain operations for several days before culmination. Depending on the attrition and expenditure of stocks, it could then require days or weeks to reset before a similar effort.
[46] Reset refers to out-of-theater replenishment, such as is required for reloading vertical launch tubes. If the reset requires repairing significant battle damage, then it could extend to months or years.
[47] This category covers a large array of capabilities for which it is difficult to make generalizations. This rating envisions a capability with a small set of personnel and equipment that could be rapidly deployed by air. Some capabilities in this category are global and so have no build-up time. Others might require technical infrastructure that could require weeks or months to put in place.
[48] Again, it is difficult to generalize about this broad array of categories. Decades of experience with EW suggests that unlike the other cycles, the reset interval will often not be the limiting factor of use. Cold War doctrine did not envision continuous jamming but intermittent use tied to the scheme of maneuver in order to maintain survivability, security, and effectiveness of EW assets.

C-5. Information environment operations (IEO).[49]

a. Information operations is the current terminology used by the Department of Defense (DoD) for operations in the information environment. To support MDO, information operations must evolve to IEO. IEO synchronizes information related capabilities (IRC), in concert with operations, to create effects in and through the information space.[50] IRC advance the commander's intent and concept of operations; seize, retain, and exploit the initiative in the information space; and consolidate gains in the information environment, to achieve a decisive information advantage over enemies and adversaries. IEO can provide commanders additional ways and means to:

- Degrade, disrupt, or destroy threat capabilities that inform or influence decision making.

- Degrade, disrupt, or destroy threat capabilities that command and control maneuver, fires, intelligence, communications, and information warfare capabilities employed against friendly forces.

- Protect friendly information, technical networks, and decision-making capabilities from an exploitation by adversary/enemy information warfare assets.

- Influence enemy formations and populations to reduce their will to fight.

- Influence friendly and neutral populations to enable friendly operations.

b. In support of MDO, IEO must be fully integrated into the planning and execution of the joint targeting process. When converged with other capabilities, IEO directly supports opening and exploiting windows of superiority during competition and armed conflict. The military capabilities that contribute to IEO which should be taken into consideration include: strategic communications, joint and interagency coordination, public affairs, civil-military operations, cyberspace operations, information assurance, space operations, military information support to operations, intelligence, military deception, operations security, EMS operations, and military and civilian engagement.

c. Commanders must understand the information space and determine how enemies and adversaries operate in that environment. Understanding begins with analyzing the adversary/enemy's use of the information space and how it employs IRC to gain an advantage. It continues with determining threat vulnerabilities that friendly forces can exploit and identifying areas which must be defended against adversary/enemy IRC.

d. IEO provides commanders an implementation strategy and integrative framework for employing IRC. An integrated IEO campaign may include the use of the cyberspace domain, the space domain, and the EMS to deliver IEO products, observe enemy or adversary actions and

[49] IEO is the integrated employment, during military operations, of information related capabilities (IRC) in concert with other lines of operations to influence, deceive, disrupt, corrupt, or usurp the decision making of enemies and adversaries while protecting our own; to influence enemy formations and populations to reduce their will to fight; and influence friendly and neutral populations to enable friendly operations.
[50] For purposes of this concept, the information space refers to the complex system of interrelated and networked information flows amongst and between populations that a commander must understand and consider to gain and maintain freedom of action.

reactions, or to deliver cyberspace, space, or EW effects. Integrating cyberspace, space, and EW capabilities generates synergistic information space effects. When employed as part of IEO that includes multiple IRC; intelligence, cyberspace, space, and EW operations can provide commanders an alternative solution to challenging operational problem sets.

C-6. Engagement[51]

a. Since war is fundamentally and primarily a human endeavor, the Joint Force working with its partners, must address the cognitive aspects of political, human, social, and cultural interactions to achieve operational and national objectives. Employing engagement, the Joint Force and its partners synchronize activities to understand, influence, and achieve human interactions which cross all domains, the EMS, and the information environment to achieve a position of relative advantage during competition or armed conflict. Engagement enables U.S. forces to outmaneuver an adversary cognitively as well as physically and virtually to deter, counter, and deny the escalation of violence in competition, and defeat the enemy if armed conflict cannot be avoided. Additionally, through engagement, routine contact and interaction between the Joint Force and its partners build trust and confidence, share information, coordinate mutual activities, and maintain influence.

b. Employing the operational tenets of engagement presents multiple dilemmas to an enemy, converging multi-domain capabilities that will create windows of superiority for friendly forces.[52] In the best case, engagement activities can strengthen U.S. options and measures in competition, and avert or deter armed conflict. However, if armed conflict cannot be avoided, engagement provides a deeper and common understanding of the operational environment, and enables opening windows of superiority and turning denied spaces into contested spaces.

c. A cognitive window of superiority is created by degrading, disrupting, or otherwise manipulating a decision maker's understanding and decision cycle or influencing a formation's or population's will to establish favorable conditions. Achieving cognitive windows of superiority requires careful consideration of the following tenets:

- Understand human factors of the operational environment[53]

- Incorporate human factors into campaign and operations planning, training, and exercises

- Build partner operational, institutional, governance, and expeditionary capabilities, and joint, interagency, and multinational partner networks

- Operate with and through joint, interagency, and multinational partners and indigenous populations to shape the operational environment and conduct security activities

[51] Engagement is the combination of physical, informational, and psychological actions taken to influence actors' decision making (moral and mental).
[52] Some examples of these dilemmas include: security cooperation activities can strengthen an ally's defensive capabilities and resolve; civil affairs operations can help influence a population positively toward U.S. presence and operations; military information support to operations can shape an enemy's will to fight; interactions with the host nation can develop valuable situational understanding.
[53] Human factors are the physical, cultural, psychological, and behavioral attributes of an individual or group that influence perceptions, understanding, and interaction.

Appendix D
MDO in Dense Urban Terrain (DUT)

D-1. Introduction

a. **Purpose.** This appendix applies MDO ideas and solutions to a dense urban terrain. It provides a description of the problems encountered in DUT and implications for MDO. The ideas and solutions found in this appendix use historical and current urban conflict analyses across a collection of sources, but are informed primarily from the Mosul Study Group Phase II literature review, research, and campaign analysis.

b. **Background.** National defense documents focus on the evolving threat and the changing character of warfare identify urbanization trends that portend future competition or conflict with the evolving threat will take place in urban environments. Particularly problematic is the potential for competition and armed conflict in megacities.[54] These areas involve diverse, interconnected human and physical networks, three-dimensional engagement areas, and terrain and infrastructure that provide varying levels of ready-made cover and concealment. Urban operations are inherently multifaceted. The scale and complexity posed by megacities challenge Army forces' capabilities and capacities to compete with, operate and fight versus prepared adversaries.

D-2. Dense urban terrain

a**. Characteristics of dense urban terrain**. Dense urban terrain possess unique characteristics that complicate all aspects of friendly and enemy operations, to include competition below the threshold of armed conflict, penetration and dis-integration of an adversary's anti-access and area denial systems, exploitation of freedom of maneuver to defeat enemy forces, and consolidation of gains. The physical characteristics (e.g., scale of urban area, urban density, and infrastructure) constrain maneuver, limit situational understanding, and create unique problems for targeting and delivering effects against enemy positions. Cognitive characteristics (e.g., degree of internal and external connectedness, demographics of the human terrain, institutions, and governance) influence political decisions, which in turn shape operations, rules of engagement, and narratives. Finally, operational characteristics in DUT (e.g., the type of enemy, degree of joint access, mission, and type of combined force) drive force and capability requirements.

(1) Physical. Physical characteristics of DUT effect all aspects of competition and armed conflict. Man-made terrain and natural barriers combine to fragment and frustrate maneuver operations. The density and diversity of structures obscure enemy positions and strength, challenge friendly communications, and, when destroyed, create rubble causing mobility and countermobility problems. Large groups of non-combatants complicate maneuver and fires operations, overwhelm rear-area capabilities, and create challenges to intelligence collection and

[54] The number of megacities (defined as metropolitan areas encompassing more than 10 million inhabitants) has doubled in the past 20 years and is projected to double again by 2050. Megacities contain populations, and exercise political, economic, and social influence comparable to many nation-states.

analysis. Each city presents its own challenges but all urban operations require extensive force commitments both for combat and stability operations.

(2) Cognitive. Cognitive considerations consist of the flow of people, goods, and data in and between dense urban areas. The interrelated flow of people, goods, and data creates environmental complexity, which congests and complicates the use of all domains, the EMS, and the information environment. The unique physical and cultural design of each urban area influences its internal flow. Function – centered on formal or informal institutions of governance – connects and informs flow relative to the rest of the country, region, or globe. The networking of urban environments on a regional or global scale has expanded the influence of population centers and the impact of urban operations on political, economic, and social systems. These characteristics present commanders and staffs with a constantly changing operational picture to assess making intelligence gathering and effects planning (lethal or nonlethal) difficult.

(3) Operational. Regardless of location or type of operation, in dense urban terrain the Army usually operates in unfamiliar and complex terrain in support of a partner force or local government objectives. This requires that the Army understand mission requirements, coalition and host nation security force capabilities, and return to competition objectives. These three considerations inform force size, logistics, and set the theater requirements. The force requirement for any mission (offense, defense, stability) is greater in DUT than in any other environment. Partner force and coalition members influence rules of engagement and determine the support or enabling capabilities required to facilitate movement and maneuver in urban areas. Finally, return to competition objectives impact consolidation of gains operations, which in DUT can require the generation of extensive stability forces.

b**. Compounding and compressing the problems**. During armed conflict, urban areas both compound the friction of war and compress physical and temporal spaces. Dense urban terrain compounds friction by combining more obstacles to maneuver (people, terrain, congested EMS and airspace) and by requiring the simultaneous execution of more tasks (airspace and fires de-confliction, protection, lethal and nonlethal fires synchronization) to enable constrained maneuver. To execute more tasks simultaneously, the Army must deploy more forces and capabilities into urban areas, which compresses the physical and temporal space available for operations. The phenomenon of increased friction and compressed space complicate the execution of core competencies, which demands greater focus and discipline from tactical and operational units. This reduces individual Soldier, unit, and staff bandwidth for the incorporation of new technologies introduced during conflict.

D-3. Operating in dense urban terrain

a. **Challenges in dense urban terrain**. There are several challenges to operating in DUT, including:

(1) Constraining offensive maneuver operations by requiring the attacker to expend force and energy either to secure lines of communications in the vicinity of a bypassed city or to enter and clear the city.

(2) Obscuring operations and forces (physical and cognitive).

(3) Increasing requirements for combat power to maintain operational reach, sustain relative advantages, prevent early culmination, and enable stability operations.

(4) Requiring the synchronization and integration of lethal and nonlethal effects in congested and contested spaces.

(5) Challenging the ability to seize the initiative, and dictate operational tempo as a result of greater friction and attrition.

(6) Sustaining friendly forces in widely dispersed locations to include providing medical and mortuary affairs support/evacuation.

b. To set politically favorable conditions for conflict, in competition an adversary will focus information warfare and unconventional warfare operations on targeted populations and influential DUT. During the transition to armed conflict, adversary forces will rapidly seize vulnerable urban areas to enable swift consolidation of gains and protection of lines of communications. Dense urban terrain's advantages thus lay in the potential for providing early warning and slowing enemy operational tempo. To capitalize on these advantages, the Army must understand, organize, and train to operate in strategically and operationally significant urban areas.

(1) Understanding dense urban terrain in competition. To best understand DUT in competition, the Army should position forces in operationally and strategically significant cities. The placement of Army forces in cities, however, is likely to cause political complications. Regardless, understanding urban areas during competition requires a grasp of the characteristics of DUT described above, and the best ways to employ urban terrain defensively during conflict. Dense urban terrain provides early warnings of enemy intent, or partner nation activities likely elicit a military response from the enemy (such as anti-Russian rallies in Kiev in 2014). Understanding the flow of people and ideas enables the Army to identify major environmental changes, which is essential to understanding DUT in competition. This level of understanding requires technical collection means, but is largely achievable through physical presence (e.g., HUMINT and SOF) and the collection of open source data, particularly from social media. By developing an understanding of the cognitive and operational characteristics of DUT during competition, the Army gains an initial advantage in armed conflict.

(2) Understanding dense urban terrain in conflict. Once conflict starts, the urban environment becomes increasingly dynamic, which quickly erodes initial advantages in understanding. Gaining or maintaining an understanding of an urban area during conflict requires considerable technical means to enable collection, analysis, and display of multi-domain data. Joint and partner nation collection means, primarily mechanical sensors, must saturate the terrain and airspace above a city. This enables collection of immense amounts of data regarding the physical, cognitive, and operational characteristics of DUT. From the large volume and various forms of collected data, intelligence analysts must synthesize and isolate information critical to operations and decision making. Then, to enable the rapid action against smaller and

easily concealed forces, mission command systems must display analyzed data in near real-time. Technical understanding of DUT in conflict serves two primary purposes. First, it provides units with situational awareness of the immediate area. Second, mechanical sensors enable intelligence collection that supports targeting and shaping operations. Establishing and maintaining situational awareness in DUT, however, consumes considerable resources, which challenges Army capability and capacity to collect and processing, exploitation, and dissemination of intelligence, which necessitate artificial intelligence-enabled processes.

(3) Organizing for operations in dense urban terrain. No single military Service or Army unit is capable of unilaterally operating in DUT during competition or conflict. During competition, the Army relies on host nation and whole-of-government approval and support for its presence and operations. During conflict, the Army supports host nation operations in urban environments to mitigate political risk and reduce operational costs for U.S. forces. Dense urban terrain operations also require considerable synchronization of joint capabilities and integration of conventional and special operations forces. Further, maneuver units must create combined arms teams with a mixture of engineer, armor, infantry, and artillery forces. This enables movement to and through urban areas, and penetration and clearance of physical structures. Disaggregated maneuver units move along splintered axes of advance and conduct distributed operations, which require more sustainment and maneuver support resources. To understand and support DUT operations, echelons above brigade must streamline processes to enable faster more precise communications, decision making, and enabler support. Finally, urban operations require extensive Joint Force generation and logistics, which depend on a robust theater army and enabling commands to set the theater during competition.

(4) Training for operations in dense urban terrain. The Army must train at echelon for urban operations. Successful urban operations are predicated on the ability to conduct three essential tasks. First, multi-domain isolation of an urban area to control logistics and communications. Second, penetration of the hardened exterior boundary and internal structures of an urban area. Third, the ability to gain and maintain contact with the enemy once inside DUT. Although effective tactical engagement is an important aspect of these tasks, operational and strategic actions ensure victory in urban battles. Field armies and corps train to manage the political conditions and operational tasks associated with isolating urban areas. Field armies and corps, in conjunction with divisions, train to plan and execute rapid maneuver operations. These units must also train to set the sustainment infrastructure required to project and maintain combat forces, should urban combat require deliberate house-to-house clearance operations. At and below the division level, maneuver units train to penetrate and operate in urban terrain. Divisions train to support maneuver units by coordinating force generation and projection, sustainment, and joint effects integration. Brigades and below train to penetrate urban terrain, and gain and maintain contact with the enemy in this complex environment.

(5) Operating in dense urban terrain. As an expeditionary force, the Army primarily operates in urban areas during natural or man-made disasters. This has conditioned the Army to visualize urban operations in conflict terms defined by minimal understanding and offensive or stability actions. Dense urban terrain, however, is increasingly a competition space, which provides the Army an opportunity to deter conflict. By operating in DUT, the Army can better understand enemy intentions and coordinate training exercises to confront aggression and

conduct IEO and special operations to deter escalation. In conflict, urban areas support defensive operations against larger, more sophisticated forces, but remain vulnerable to isolation. During offensive operations, DUT constrains maneuver and slows operational tempo requiring additional forces. Finally, stabilizing or consolidating gains in urban areas, particularly partner nation capitals and DUT surrounding critical air and sea ports, is essential to securing lines of communications and political support for all operations.

c. **The tenets of MDO applied in dense urban terrain.**

(1) Calibrate force posture. Calibrated force posture for DUT operations requires preparation during competition. Actions in competition focus on visualizing urban environments in enough detail to anticipate their unique force generation, sustainment, and intelligence requirements during conflict. This enables theater and field armies to effectively set the theater.

(a) Forces. U.S. forces must focus on prepositioning theater enabling commands (TEC) that support intelligence, fires (lethal and nonlethal), sustainment, and mission command functions. Intelligence and Security Command (INSCOM) is the Army's operational intelligence arm. Through the Military Intelligence Brigade-Theater (MIB-T), INSCOM enables the geographic combatant command (GCC) to focus collection efforts on operationally and strategically significant urban areas. Lethal and nonlethal fires TEC allow GCC to synchronize joint effects during initial phases of conflict operations. Operational control measures that will be required to converge lethal and nonlethal fires in DUT areas can be established and rehearsed in competition. Sustainment TEC develop pre-conflict estimates and pre-coordinate contracting requirements needed to maintain forces executing deliberate urban operations. Finally, mission command requires headquarters elements to command and control, exercise authority, and provide direction. Signal TEC provide the network capability and capacity to support coalition operations in congested and contested communications space. Signal TEC also enable the distribution of massive amounts of intelligence and information flowing from the DUT. Setting the theater with enough intelligence, fires, sustainment, and mission command capability provides GCC with the capacity to visualize critical urban areas during competition, and transition to conflict when required.

(b) Footprint. An increase in forward presence forces requires a commensurate increase in the forward footprint (facilities). Basing and infrastructure to accommodate in-theater forces must enable joint and combined operations in urban operations. APS also need to be evaluated and adjusted to support U.S., partner, or allied maneuver, fires, sustainment, and force protection operations in urban areas.

(c) Agreements. Agreements with partner nations and allies must account for force and footprint requirements, and for increased intelligence and information gathering activities in specific urban areas. If U.S. forces intend to understand DUT during competition, activities such as IPB or operational preparation of the environment will increase and likely require Department of the State awareness, if not concurrence. IPB or operational preparation of the environment is best conducted in collaboration with the host nation. Additionally, joint and coalition forces must establish urban specific rules of engagement during competition to inform set the theater requirements and enable a rapid transition to armed conflict.

(2) Multi-domain formations. Since dense urban terrain operations attrit forces at a higher rate than operations in other environments, formations, systems, and Soldiers that provide the combination of capacity, capability, and endurance necessary to operate across multiple domains in contested spaces against a near-peer adversary are required. Independent maneuver enables quicker adaptation by units operating in a constantly evolving DUT. Cross-domain fires integrates and delivers lethal and nonlethal fires across all domains, the EMS, and the information environment effecting the physical, cognitive, and operational characteristics present within DUT. Finally, each combatant in urban operations exerts constant physical and psychological pressure on its adversary. The Army requires human dimension research that enables mitigation of these impacts on friendly forces while increasing, particularly, the psychological impact of urban operations on the enemy.

(3) Convergence. The advantages of convergence, creation of cross-domain synergy and the layering of options, apply equally in DUT. Implementation of convergence, however, may be challenged by complex and congested physical and virtual environments and potential restrictions of rules of engagement. There may be increased use of nonlethal effects, and not all lethal effects may be useable.

D-4. Conclusion

Urban environments are inherently multi-domain. The interconnectedness of urban areas enables the flow of information, people, and commodities that make this environment disproportionately influential to all human affairs, including armed conflict. Dense urban terrain compresses physical and temporal spaces, compounds obstacles, and demands the simultaneous execution of multiple tasks. This means that while operations are slowed, the pace and complexity of tactical engagements increases. Employing the components of MDO in conjunction with improvements in Army capacity and capability to understand, organize, and train to operate in DUT enables successful operations.

Appendix E
Linkage to other concepts

E-1. This concept has linkages to the following concepts: Capstone Concept for Joint Operations, A Cooperative Strategy for 21st Century Seapower, Marine Corps Operating Concept: How an Expeditionary Force Operates in the 21st Century, Air Superiority 2030 Flight Plan, Air Force Future Operating Concept, Joint Concept for Integrated Campaigning (JCIC), Joint Operational Access Concept (JOAC), Joint Concept for Access and Maneuver in the Global Commons (JAM-GC), Joint Concept for Entry Operations (JCEO), Joint Concept for Human Aspects of Military Operations (JC-HAMO), and Joint Concept for Rapid Aggregation.

E-2. The Capstone Concept for Joint Operations establishes globally integrated operations as the future joint operational concept designed to address the challenge of meeting unremitting strategic requirements with constrained military resources. This concept describes how the Joint Force, and particularly ground forces, will overcome current challenges for rapid aggregation of globally distributed forces to conduct globally integrated operations.

E-3. A Cooperative Strategy for 21st Century Seapower states that naval forces perform these essential functions: all-domain access, deterrence, sea control, power projection, and maritime security. The *U.S. Army Multi-Domain Operations* concept proposes joint approaches that help address these essential functions.

E-4. The Marine Corps Operating Concept: How an Expeditionary Force Operates in the 21st Century focuses on five key drivers of change: complex terrain, technology proliferation, information as a weapon, battle of signatures, and increasingly contested maritime domain. The *U.S. Army Multi-Domain Operations* concept proposes joint approaches that help address these changes.

E-5. Air Superiority 2030 Flight Plan states that developing and delivering air superiority for the highly contested environment in 2030 requires a multi-domain focus on capabilities and capacity.

E-6. The Air Force Future Operating Concept states that flexibility in operational agility manifests as integrated MDO. It further asserts that operationally agile forces will defeat future enemy threats by fighting in a highly coordinated manner under the principle of mission command, and that this approach must be developed within the framework of the joint and combined team.

E-7. The Joint Concept for Integrated Campaigning (JCIC) describes a complex operational environment in which the Joint Force continually campaigns within the competition continuum, which features some mixture of cooperation, competition below armed conflict, and armed conflict. Within this construct, the purpose of the Joint Force is to continually seek the maintenance and sustainment of strategic aims, while countering efforts of revisionist states to undermine U.S. interests. MDO offers the means for the Joint Force to more effectively campaign across the competition continuum.

E-8. The Joint Operational Access Concept (JOAC) identifies the problem of projecting military force into an operational area and sustaining it in the face of armed opposition by increasingly capable enemies and within contested domains. The JOAC proposes employing cross-domain synergy – the complementary vice merely additive employment of capabilities in different domains such that each enhances the effectiveness and compensates for the vulnerabilities of the others – to establish superiority in some combination of domains that will provide the freedom of action required by the mission. This concept shows how ground forces will help to obtain cross-domain synergy in support of the joint campaign.

E-9. The Joint Concept for Access and Maneuver in the Global Commons (JAM-GC) states that the future force must be distributable, resilient, and tailorable, with sufficient scale and capable of operations of ample duration. The JAM-GC's solution includes advanced integration of operations across multiple domains, both inside and outside the contested environment. This is consistent with many of the ideas in this paper. This concept expands JAM-GC's premises from the global commons to operational maneuver by combined arms formations on land, integrated with those in the air, maritime, cyberspace, and space domains.

E-10. The Joint Concept for Entry Operations (JCEO) focuses on the integration of force capabilities across domains in order to secure freedom of maneuver on foreign territory within an operational area. This concept complements and helps set conditions for the operational ideas in the JCEO.

E-11. The Joint Concept for Human Aspects of Military Operations (JC-HAMO) supports the *U.S. Army Multi-Domain Operations* concept's need to understand relevant actors' motivations and the underpinnings of their will. JC-HAMO acknowledges the centrality of human will in war and provides a framework that integrates with the commander's decision cycle, enabling the Joint Force to influence a range of relevant actors. The goal of this concept is to improve understanding and effectiveness for cognitive activities during the conduct of operations.

E-12. The Joint Concept for Rapid Aggregation seeks to improve the speed, effectiveness, and efficiency of Joint Force aggregation in support of globally integrated operations. It describes the idea of forming operationally coherent joint and combined forces by quickly combining forces and capabilities, internally and with mission partners, across domains, echelons, geographic boundaries, and organizational affiliations. MDO complements this with the idea of dynamically calibrating force posture.

Appendix F
Lessons learned from the fielded force

F-1. Lessons to inform the *U.S. Army Multi-Domain Operations* concept
The Army has begun a rigorous process of experimentation and analysis to further inform and refine the *U.S. Army in Multi-Domain Operations* concept. In 2017, the Chief of Staff of the Army (CSA) directed the design and testing of Multi-Domain Task Forces (MDTFs) as forward-stationed formations able to execute aspects of MDO. Designed to deliver long-range precision joint strike as well as integrate air and missile defense, electronic warfare, space, cyber, and information operations, the MDTF operates across all domains, the EMS, and the information environment in both competition and conflict to provide the Joint Force and coalition with new capabilities to enable the defeat adversaries' anti-access and area denial strategies. Given its capability to compete and provide and initial penetration, the MDTF, as a forerunner to other multi-domain formations now in development, is the essential first step to realizing an MDO-capable Army by 2028.

a. U.S. Army Pacific is building the first experimental MDTF and executing a multi-year joint and combined experimentation program to inform future MDTF design. This experiment combines 17th Field Artillery Brigade with an augmented headquarters element, a joint intelligence, cyberspace, electronic warfare, and space (ICEWS) component, and other tasked organized formations to provide realistic assessments of concepts and capabilities and gather warfighter feedback to inform both Army plans and concept development. Forward stationed MDTFs with capabilities in all domains, the EMS, and the information environment create new dilemmas for adversaries that strengthen deterrence by complicating potential enemy war plans. During conflict, MDTFs also enable successful combat operations through early attrition of the adversary's anti-access and area denial systems and supporting combat forces from the inside, thereby re-enabling joint and combined maneuver held at risk today. Over numerous experiments and exercises in 2018, the MDTF successfully linked systems and Services across all domains, the EMS, and the information environment in ways never previously accomplished. Joint and combined components demonstrated new ways to share surveillance and targeting capabilities in support of combined schemes of maneuver. Most significantly, the MDTF demonstrated methods of employing layered non-kinetic effects (EW, space, cyberspace, and information operations) that helped set the conditions for successful combined kinetic engagements against both maritime and airborne targets. U.S. Army Pacific's efforts have provided critical lessons for both the Army and the Joint Force and are enabling faster, and effective transitions of MDO from concept to fielded capabilities.

b. Joint Warfighter Assessment (JWA) is the Army's capstone multi-echelon live and constructive exercise intended to demonstrate and assess future force concepts and capabilities required for a more lethal, expeditionary, and agile force. JWA exercises establish the conditions to assess unit execution of the MDO concept, ensure integration and interoperability of joint and multinational partners, and integrate and assess future force concepts and capabilities. To achieve an MDO-capable Army by 2028, JWA exercises provide the Army with valuable opportunities to focus the approach to "operationalizing MDO." These exercises allow for multi-echelon participants to experiment with the conceptual component solutions and to mature enabling capabilities to solve the five key problems of the MDO fight against a peer

adversaries: how does the Joint Force compete, penetrate, disintegrate, exploit, and re-compete throughout the depth of the operational environment to fight, win, and survive. JWA 18-1 was the first, examining MDO ideas at Grafenwoehr, Germany, between 27 April and 10 May 2018.

F-2. Lessons learned – tenets of MDO

a. **Calibrated force posture**. To effectively compete against a near-peer adversary, the Joint Force requires forward deployed multi-domain formations that operate within the range of an adversary's long-range anti-access and area denial systems. As a component of the Joint Force, the Army presents a reasonable option to provide an enduring and resilient posture in areas contested by an adversary's actions in competition and armed conflict.

(1) Ideally, these formations would represent the Army component of a permanent or virtual CJTF that develops habitual training relationships. These Army formations, however, must also have the capability to execute independent maneuver and employ cross-domain fires based on the Joint Force Commander's intent in cases where command and control capabilities are severely degraded. Multi-domain formations would also employ movement and maneuver throughout the theater in the competition phase and conduct capabilities demonstrations in support of deterrence, influence operations, and military deception plans.

(2) Non-kinetic effects are increasingly important in setting the conditions for successful kinetic operations by creating a relative advantage, particularly when force ratios favor an adversary. Effects such as denial and disruption of enemy communications, surveillance, tracking, navigation capabilities, the introduction of false information into enemy networks, and influence operations will be increasingly important factors of successful kinetic engagements. These can only be provided by forward deployed forces operating within areas or regions contested by an adversary.

b. **Multi-domain formations**.

(1) Wargames and simulations indicate that ground forces are relatively survivable (compared to air and naval forces) operating deep within an adversary's anti-access and area denial threat zone, provided they employ a layered set of protective measures. These measures include dispersal; a robust mobility plan; strict emissions control until certain trigger criteria are met; camouflage, concealment, and deception (including electromagnetic deception); and mobile mission command. Multi-domain formations provide a decisive contribution to the Joint Force by immediately contesting enemy aggression and conducting the initial penetration of enemy long-range systems from inside the range of their anti-access and aerial denial systems.

(2) Training and evaluating Soldiers and leaders in executing MDO will require state of the art real-time wargame simulation capabilities that include other Service, interagency, and multinational partner capabilities.

c. **Convergence**. Convergence is achieved both through Service-centric and joint integration of capabilities in all domains, the EMS, and the information environment. Schemes for Service-

centric integration are well-advanced. The Joint Force, however, has important shortfalls in its capability to achieve Joint convergence. Some shortfalls are technical, others are conceptual.

(1) Technical shortfalls. Two of the most important technical shortfalls are the lack of a joint common operational picture (COP) and limitations in joint sensor-to-shooter loop functionality. The Joint Force requires a COP, or visualization and decision support tool, which allows commanders in any Service, at any echelon, in any mission area, and at any classification level to "down-select" the categories of information they need to make informed decisions. It should also include the technical means to get that information pushed to them from all supporting components. The joint and combined team also require the capability for any joint sensor to publish surveillance and targeting data so it is available to any joint shooter, kinetic or non-kinetic. Army multi-domain formations must have the capability, for example, to receive targeting data and clearance of fires from joint platforms such as the F-35, Aegis, or from other Theater or National Technical Means. The Army and the other Services have many programs and initiatives underway that can help close these shortfalls.

(2) Conceptual shortfalls.

(a) Mission command. The Army must continue to build trusted teams of professionals that thrive in ambiguity and chaos and who are empowered through a doctrine of mission command to rapidly react to threats and opportunities based on a commander's intent. The MDO concept leverages a critical U.S. military advantage—our people. But the Army does not always design our training programs and exercises in ways that facilitate or require this type of decentralized decision making. More intellectual effort is required to improve training designs that facilitate mission command of MDO given the increased complexity.

(b) Authorities. Many of the most important non-kinetic capabilities across the Joint Force are compartmented, and only a small number of staff at the theater headquarters level are authorized access. Many of these same programs require authorization to employ a capability at the Secretarial level or higher and/or authorization from a functional combatant command. The Joint Force needs to put in place and exercise processes to rapidly obtain approval to employ these capabilities in support of tactical operations (i.e., below Corps, Fighter Wing, Carrier Strike Group, and Marine Expeditionary Force). This is particularly critical when force ratios favor an adversary.

(c) Munitions optimization planning. Limited inventories of munitions across the Joint Force could create critical shortfalls that lead to defeat in combat. Therefore, when multiple joint fires systems are in kinetic range of the same adversary threats, munitions plans that optimize and sequence fires can help husband limited resources while achieving desired effects. An integrated munitions optimization plan is required in addition to de-confliction mechanisms.

F-3. Lessons learned – materiel modernization

While DoD once dominated virtually all technological development related to combat operations, today the commercial sector is producing many combat enabling technologies faster than DoD. In some areas, DoD acquisition processes almost guarantee the obsolescence of equipment by the time it is fielded. Ongoing acquisition reforms efforts recommend the Army

consider selective fielding of new capabilities that are Acquisition Category II or III and adopt the "Buy, Try, Decide" model pioneered by U.S. Special Operations Command. This will help ensure Army formations remain equipped with state of the art capabilities to meet their mission requirements and will allow the Army to better assess what emerging capabilities should become new Army programs of record or which might inform change proposals to current programs of record.

Appendix G
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Required References. Army regulations, Department of the Army pamphlets, field manuals (FMs), Army doctrine publications, Army doctrine reference publications (ADRP), and Department of the Army forms are available at Army Publishing Directorate home page http://www.usapa.army.mil TRADOC publications and forms are available at TRADOC Administrative Publications home page at http://adminpubs.tradoc.army.mil. Joint publications (JPs) are available on the Joint Electronic Library at http://www.dtic.mil/doctrine/new_pubs/jointpub_operations.htm or https://jdeis.js.mil/jdeis/index.jsp?pindex=0

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Glossary

Section I
Abbreviations

ADRP	Army doctrine reference publication
APS	Army prepositioned stocks
DoD	Department of Defense
DUT	dense urban terrain
EMS	electromagnetic spectrum
EW	electronic warfare
FM	field manual
HUMINT	human intelligence
IADS	integrated air defense system
IEO	information environment operations
IRC	information-related capability
ISR	intelligence, surveillance, and reconnaissance
JAM-GC	Joint Concept for Access and Maneuver in the Global Commons
JCEO	Joint Concept for Entry Operations
JCIC	Joint Concept for Integrated Campaigning
JOAC	Joint Operational Access Concept
JP	joint publication
LRPF	long-range precision fires
MDO	Multi-Domain Operations
MDTF	Multi-Domain Task Force
MRL	multiple rocket launcher
NATO	North Atlantic Treaty Organization
SOF	special operations forces
SAM	surface-to-air missile
SRBM	short-range ballistic missile
TEC	theater enabling command
TRADOC	U.S. Army Training and Doctrine Command
UAS	unmanned aircraft system
U.S.	United States

Section II
Terms

adversary
A party acknowledged as potentially hostile to a friendly party and against which the use of force may be envisaged. (JP 3-0)

air domain
The atmosphere, beginning at the Earth's surface, extending to the altitude where its effects upon operations become negligible. (JP 3-30)

armed conflict
When the use of violence is the primary means by which an actor seeks to satisfy its interests. (JCIC)

battlefield*
The area where military operations are conducted to achieve military goals consisting of all domains (air, land, maritime, space, and cyberspace), the electromagnetic spectrum, and the information environment (including human cognitive aspects). It includes factors and conditions that must be understood to successfully apply combat power, protect the force, or complete the mission including enemy and friendly armed forces, infrastructure, weather, and terrain within the operational areas and areas of interest.

calibrated force posture*
The combination of position and the ability to maneuver across strategic distances. It includes, but is not limited, to basing and facilities, formations and equipment readiness, the distribution of capabilities across components, strategic transport availability, interoperability, access, and authorities.

campaign
A series of related major operations aimed at achieving strategic and operational objectives within a given time and space. (JP 5-0)

Close Area*
Where friendly and enemy formations, forces, and systems are in imminent physical contact and contest for control of physical space in support of campaign objectives.

competition
The condition when two or more actors in the international system have incompatible interests but neither seeks to escalate to open conflict in pursuit of those interests. While violence is not the adversary's primary instrument in competition, challenges may include a range of violent instruments including conventional forces with uncertain attribution to the state sponsor. (JCIC)

contested spaces*
Those areas where U.S., allied, or coalition forces can challenge the adversary's denial measures, maintain some degree of friendly freedom of action, and potentially deny adversary freedom of action.

convergence*
Rapid and continuous integration of capabilities in all domains, the electromagnetic spectrum, and information environment that optimizes effects to overmatch the enemy through cross-domain synergy and multiple forms of attack all enabled by mission command and disciplined initiative.

counterinsurgency
Comprehensive civilian and military efforts designed to simultaneously defeat and contain insurgency and address its root causes. (JP 3-34)

cross-domain*
Having an effect from one domain into another.

cross-domain fires*
The integration and delivery of lethal and nonlethal fires across all five domains (land, maritime, air, space and cyberspace), the electromagnetic spectrum, and the information environment.

cross-domain maneuver
The employment of mutually supporting lethal and nonlethal capabilities of multiple domains to create conditions designed to generate overmatch, present multiple dilemmas to the enemy, and enable Joint Force freedom of movement and action. (TRADOC Pamphlet 525-3-6)

cross-domain synergy
The complementary vice merely additive employment of capabilities in different domains such that each enhances the effectiveness and compensates for the vulnerabilities of the others – to establish superiority in some combination of domains that will provide the freedom of action required by the mission. (Capstone Concept for Joint Operations, JOAC)

cyberspace
A global domain within the information environment consisting of the interdependent networks of information technology infrastructures and resident data, including the Internet, telecommunications networks, computer systems, and embedded processors and controllers. (JP 3-12)

cycle time*
The shortest overall time required to complete one full linkage of preparation, planning and execution, duration, and reset of a capability.

decisive operation
The operation that directly accomplishes the mission. (ADRP 3-0)

decisive space*
Conceptual geographic and temporal location where the full optimization of the employment of cross-domain capabilities generates a marked advantage over an enemy and greatly influences the outcome of an operation.

Deep Fires Areas*
The areas beyond the feasible range of movement for conventional forces but where joint fires, SOF, information, and virtual capabilities can be employed.

Deep Maneuver Area*
The area where maneuver forces can go (beyond the Close Area) but is so contested that maneuver still requires significant allocation and convergence of multi-domain capabilities.

destroy
Tactical mission task that physically renders an enemy force combat ineffective until it is reconstituted. Alternatively, to destroy a combat system is to damage it so badly that it cannot

perform any function or be restored to a usable condition without being entirely rebuilt. (FM 3-90-1)

denied spaces*
Those areas where the adversary can severely constrain U.S. and allied forces' freedom of action through anti-access and area denial and other measures.

dense urban terrain*
Areas characterized by extraordinarily closely-packed manmade infrastructure and high population density, potentially including concentrations of high-rise buildings, subterranean features, and densely packed slums.

dis-integrate*
Break the coherence of the enemy's system by destroying or disrupting its subcomponents (such as command and control means, intelligence collection, critical nodes, etc.) degrading its ability to conduct operations while leading to a rapid collapse of the enemy's capabilities or will to fight.

dislocate*
Render the enemy's strength irrelevant (and ill positioned) by achieving positional advantage through movement, removing the enemy from the decisive point, or achieving functional advantage through technology or tactics. (proposed change to existing doctrinal term)

domain*
An area of activity within the operational environment (land, air, maritime, space, and cyberspace) in which operations are organized and conducted. (modified joint definition)

echeloning or **echelonment***
Maneuver of forces from the Strategic and Operational Support Areas into the Tactical Support Area and Close Area.

electromagnetic spectrum
The range of frequencies of electromagnetic radiation from zero to infinity. It is divided into 26 alphabetically designated bands. (JP 3-13.1)

enemy
A party identified as hostile against which the use of force is authorized. (ADRP 3-0)

engagement*
The combination of physical, informational, and psychological actions taken to build relationships or influence actors' decision-making (moral and mental).

escalation advantage*
The ability to change the correlation of forces in your favor faster than an adversary.

expeditionary maneuver*
The rapid deployment of task-organized combined arms forces able to transition quickly to conduct operations of sufficient scale and ample duration to achieve strategic objectives.

fix
A tactical mission task where a commander prevents the enemy from moving any part of his force from a specific location for a specific period. Fix is also an obstacle effect that focuses fire planning and obstacle effort to slow an attacker's movement within a specified area, normally an engagement area. (FM 3-90-1)

globally integrated operations
Operations arranged as cohesive military actions in time, space, and purpose, executed as a whole to address transregional, all domain, and multi-functional challenges. (Capstone Concept for Joint Operations (draft-2018))

hyperactive*
More active than usual or desirable; hyper-competitive during competition and hyper-violent in armed conflict.

independent maneuver*
Operating dispersed for an extended period without continuous [or contiguous] support from higher echelons while retaining the ability to concentrate combat power rapidly at decisive spaces by employing cross-domain fires and maneuver to achieve mission objectives within the intent of the theater campaign.

information space*
The complex system of interrelated and networked information flows amongst and between populations that a commander must understand and consider to gain and maintain freedom of action.

information environment
The aggregate of individuals, organizations, and systems that collect, process, disseminate, or act on information. (JP 3-13)

information environment operations*
Integrated employment of information related capabilities (IRC) in concert with other lines of operation to influence, deceive, disrupt, corrupt, or usurp the decision making of enemies and adversaries while protecting our own; to influence enemy formations and populations to reduce their will to fight; and influence friendly and neutral populations to enable friendly operations.

information operations
Integrated employment, during military operations, of information related capabilities (IRC) in concert with other lines of operation to influence, deceive, disrupt, corrupt, or usurp the decision making of enemies and adversaries while protecting our own. (JP 3-13)

information warfare
Employing information capabilities in a deliberate disinformation campaign supported by actions of the intelligence organizations designed to confuse the enemy and achieve strategic objectives at minimal cost.[55]

interoperability
The ability to operate in synergy in the execution of assigned tasks. (JP 3-0) 2. The condition achieved among communications-electronics systems or items of communications-electronics equipment when information or services can be exchanged directly and satisfactorily between them and/or their users. (JP 6-0)

intelligence, surveillance, and reconnaissance
An integrated operations and intelligence activity that synchronizes and integrates the planning and operation of sensors, assets, and processing, exploitation, and dissemination systems in direct support of current and future operations. Also called ISR. (JP 2-01)

irregular warfare
A violent struggle among state and non-state actors for legitimacy and influence over the relevant population(s). Also called IW. (JP 1) [Note: Irregular warfare favors indirect and asymmetric approaches, though it may employ the full range of military and other capacities, to erode an adversary's power, influence, and will.]

isolate
A tactical mission task that requires a unit to seal off—both physically and psychologically— an enemy from sources of support, deny the enemy freedom of movement, and prevent the isolated enemy force from having contact with other enemy forces. (FM 3-90-1)

land domain
The area of the Earth's surface ending at the high water mark and overlapping with the maritime domain in the landward segment of the littorals. (JP 3-31)

littoral
The littoral comprises two segments of the operational environment: 1. Seaward: the area from the open ocean to the shore, which must be controlled to support operations ashore. 2. Landward: the area inland from the shore that can be supported and defended directly from the sea. (JP 2-01.3)

maritime domain
The oceans, seas, bays, estuaries, islands, coastal areas, and the airspace above these, including the littorals. (JP 3-32)

multi-domain*
Dealing with more than one domain at the same time.

[55] Derived from Russia Report I, pg 9. Adapts Soviet reflexive control to the contemporary geopolitical context. "Reflexive control" is defined as a means of conveying to a partner or an opponent specially prepared information to incline him to voluntarily make the predetermined decision desired by the initiator of the action.

multi-domain formations*
Army organizations possessing the combination of capacity, capability, and endurance necessary to operate across multiple domains in contested spaces against a near-peer adversary.

Multi-Domain Operations (MDO)*
Operations conducted across multiple domains and contested spaces to overcome an adversary's (or enemy's) strengths by presenting them with several operational and/or tactical dilemmas through the combined application of calibrated force posture; employment of multi-domain formations; and convergence of capabilities across domains, environments, and functions in time and spaces to achieve operational and tactical objectives.

near-peer adversaries*
Those nation states with the intent, capabilities, and capacity to contest U.S. interests globally in most or all domains, the EMS, and the information environment.

neutralize
A tactical mission task that results in rendering enemy personnel or materiel incapable of interfering with a particular operation. (FM 3-90-1)

operational maneuver*
Maneuver that supports operational level objectives; usually occurs within a theater of operations (intratheater)

operational preparation of the environment
The conduct of activities in likely or potential areas of operations to prepare and shape the operational environment. (JP 3-05)

Operational Support Area*
The area of responsibility from which most of the air and maritime capabilities derive their source of power, control, and sustainment as well as where ground forces enter theater, organize, and prepare for rapid onward movement and integration.

overmatch*
The application of capabilities or unique tactics either directly or indirectly, with the intent to prevent or mitigate opposing forces from using their current or projected equipment or tactics.

planning and execution time*
The time required to plan employment and then execute it to create an effect, to include creating a window of advantage. Typically, planning and preparation occur simultaneously though depending on the situation and capability one or the other might be the limiting factor.

position of relative advantage
A location or the establishment of a favorable condition within the area of operations that provides the commander with temporary freedom of action to enhance combat power over an

enemy or influence the enemy to accept risk and move to a position of disadvantage. (ADRP 3-0)

precision logistics*
The art of delivering support forward utilizing a combination of sensor-driven predictive analysis, condition-based maintenance at the point of need, and robotic autonomous delivery combined with the beneficial results of demand reduction to enable multi-domain formations to present a credible deterrence during competition, to transition to armed conflict with speed and agility, and to execute Multi-Domain Operations in depth, including resupply of formations conducting independent maneuver to extend time and reach of protracted operations.

preparation time*
The time required to organize and maneuver forces or capabilities (e.g. a cyber weapon) from its current location to the intended employment space or window of advantage.

reset
A set of actions to restore equipment to a desired level of combat capability commensurate with a unit's future mission. (JP 4-0)

resilience*
The ability for Army formations and systems at all echelons to operate in contested spaces against a capable adversary

shaping operation
An operation that establishes conditions for the decisive operation through effects on the enemy, other actors, and the terrain. (ADRP 3-0)

snap drill*
Rapid reaction military exercise to test combat readiness.

space domain
The area above the altitude where atmospheric effects on airborne objects become negligible. (JP 3-14)

stand-off*
The physical, cognitive, and informational separation that enables freedom of action in any, some, or all domains, the electromagnetic spectrum, and information environment to achieve strategic and/or operational objectives before an adversary can adequately respond. It is achieved with both political and military capabilities.

strategic maneuver*
Maneuver that supports strategic level objectives; usually occurs across more than one theater of operations (intertheater)

Strategic Support Area*
The area of cross-combatant command coordination, strategic sea and air lines of communications, and the homeland.

system
A group of interacting, interrelated, and interdependent components or subsytems that form a complex and unified whole. Systems have a purpose with their parts arranged in a way (structure) to carry out their purpose. (TRADOC Pamphlet 525-3-3)

Tactical Support Area*
The area that directly enables decisive tactical operations in the Close Area and extension of capabilities into the Deep Maneuver and Deep Fires Areas.

unconventional warfare
Activities conducted to enable a resistance movement or insurgency to coerce, disrupt, or overthrow a government or occupying power by operating through or with an underground, auxiliary, and guerrilla force in a denied area. Also called UW. (JP 3-05.1)

window of superiority*
Converging capabilities in time and space in selected domains and environments to enable commanders to gain localized control or physical, virtual, and/or cognitive influence over a specified area to prevent its use by an enemy or to create conditions necessary for successful friendly operations.

* Proposed definition.

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The U.S. Army in Multi-Domain Operations 2028

EXHIBIT 54

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

Prepared by the U.S. Public Health Service Working Group
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Update: Interim Statement Regarding Potential Fetal Harm from Exposure to Dolutegravir – Implications for HIV Postexposure Prophylaxis (PEP). Please see attached file.

Summary

This report updates U.S. Public Health Service recommendations for the management of health-care personnel (HCP) who have occupational exposure to blood and/or other body fluids that might contain human immunodeficiency virus (HIV). Although the principles of exposure management remain unchanged, recommended HIV postexposure prophylaxis (PEP) regimens and the duration of HIV follow-up testing for exposed personnel have been updated. This report emphasizes the importance of primary prevention strategies, the prompt reporting and management of occupational exposures; adherence to recommended HIV PEP regimens when indicated for an exposure; expert consultation in management of exposures; follow-up of exposed HCP to improve adherence to PEP; and careful monitoring for adverse events related to treatment, as well as for virologic, immunologic and serologic signs of infection. To ensure timely postexposure management and administration of HIV PEP, clinicians should consider occupational exposures as urgent medical concerns, and institutions should take steps to ensure that staff are aware of both the importance of, and the institutional mechanisms available for, reporting and seeking care for such exposures.

Summary of Recommendations

---PEP is recommended when occupational exposures to HIV occur.

---Determine the HIV status of the exposure source patient to guide need for HIV PEP, if possible.

---Start PEP medication regimens as soon as possible after occupational exposure to HIV and continue them for a 4-week duration.

---New Recommendation--- PEP medication regimens should contain 3 (or more) antiretroviral drugs (listed in appendix A) for all occupational exposures to HIV.

---Expert consultation is recommended for any occupational exposures to HIV and at a minimum for situations described in Box 1.

---Provide close follow-up for exposed personnel (Box 2) that includes counseling, baseline and follow-up HIV testing, and monitoring for drug toxicity. Follow-up appointments should begin within 72 hours of an HIV exposure.

---New Recommendation--- If a newer 4th generation combination HIV p24 antigen-HIV antibody test is utilized for follow-up HIV testing of exposed HCP, HIV testing may be concluded at 4 months after exposure (Box 2). If a newer testing platform is not available, follow-up HIV testing is typically concluded at 6 months after an HIV exposure.

Introduction

Preventing exposures to blood and body fluids (i.e., 'primary prevention') is the most important strategy for preventing occupationally acquired human immunodeficiency virus (HIV) infection. Both individual healthcare providers and the institutions that employ them should work to ensure adherence to the principles of "Standard Precautions,"(1) including assuring access to and consistent use of appropriate work practices, work practice controls, and personal protective equipment. For instances in which an occupational exposure has occurred, appropriate postexposure management is an important element of workplace safety. This document provides updated recommendations concerning the management of occupational exposures to HIV.

The use of antiretrovirals as postexposure prophylaxis (PEP) for occupational exposures to HIV was first considered in guidelines issued by the Centers for Disease Control and Prevention (CDC) in 1990.(2) In 1996, the first U.S. Public Health Service (PHS) recommendations advocating the use of PEP after occupational exposure to HIV were published; these recommendations have been updated three times.(3-6) Since publication of the most recent guidelines in 2005, several new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and additional information has become available regarding both the use and safety of agents previously recommended for administration for HIV PEP.

As a direct result of 7 years' experience with the 2005 guidelines, several challenges in the interpretation and implementation of those guidelines have been identified. Those challenges include difficulties in determining levels of risk of HIV transmission for individual exposure incidents; problems determining the appropriate use of two- versus three- (or more) drugs in PEP regimens; the high frequency of side effects and toxicities associated with administration of previously recommended drugs; and the initial management of healthcare personnel (HCP) with exposures to a source patient whose HIV infection status was unknown. The PHS working group has attempted to address both the new information that has been developed as well as the challenges associated with the practical implementation of the 2005 guidelines in this update.

This report encourages using HIV PEP regimens that are optimally tolerated, eliminates the recommendation to assess the level of risk associated with individual exposures to determine the

number of drugs recommended for PEP, modifies and expands the list of antiretroviral medications that can be considered for use as PEP, and offers an option for concluding HIV follow-up testing of exposed personnel earlier than 6 months postexposure. This report also continues to emphasize the following: 1) primary prevention of occupational exposures; 2) prompt management of occupational exposures and, if indicated, initiation of PEP as soon as possible after exposure; 3) selection of PEP regimens that have the fewest side-effects and are best tolerated by prophylaxis recipients; 4) anticipating and preemptively treating side effects commonly associated with taking antiretroviral drugs; 5) attention to potential interactions involving both drugs that could be included in HIV PEP regimens, as well as other medications that PEP recipients might be taking; 6) consultation with experts on postexposure management strategies (especially determining whether an exposure has actually occurred and selecting HIV PEP regimens, particularly when the source patient is antiretroviral treatment-experienced); 7) HIV testing of source patients (without delaying PEP initiation in the exposed provider) using methods that produce rapid results; and 8) counseling and follow-up of exposed HCP.

Recommendations concerning the management of occupational exposures to hepatitis B virus and/or hepatitis C virus have been published previously(5, 7) and are not included in this report. Recommendations for nonoccupational (e.g., sexual, pediatric, and perinatal) HIV exposures also have been published previously.(8-10)

Methods

In 2011, the Centers for Disease Control and Prevention (CDC) reconvened the interagency U.S. Public Health Service (PHS) working group to plan and prepare an update to the 2005 *U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*.(6) The PHS working group^ was comprised of members from CDC, FDA, the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Names, credentials, and affiliations of the PHS working group are listed in the "U.S. Public Health Service Working Group" section at the end of this

guideline. The working group met twice a month to monthly to create a plan for the update as well as draft the guideline.

A systematic review of new literature that may have become available since 2005 was not conducted; however, an initial informal literature search did not reveal human randomized trials demonstrating superiority of two- versus three- (or more) drug antiretroviral medication regimens as PEP or an optimal PEP regimen for occupational exposures to HIV. Because of the low risk for transmission associated with occupational exposures (i.e., approximately 0.3% per exposure when all parenteral exposures are considered together),(11) neither the conduct of a randomized trial assessing efficacy nor the conduct of trials assessing the comparative efficacy of two- versus three-drug regimens for postexposure prophylaxis is practical. In light of the absence of such randomized trials, CDC convened a meeting of the PHS interagency working group and an expert panel of consultants* in July 2011 to discuss the use of HIV PEP, and develop the recommendations for this update. The expert panel consisted of professionals in academic medicine considered to be experts in the treatment of HIV-infected individuals, the use of antiretroviral medications, and PEP. Names, credentials, and affiliations of the expert panel of consultants are listed in the "Expert Panel Consultants" section at the end of this guideline.

Prior to the July 2011 meeting, the meeting participants^* were provided an electronic copy of the 2005 guidelines, asked to review them, and to consider the following topics for discussion at the upcoming meeting: (1) the challenges associated with the implementation of the 2005 guidelines, (2) the role for ongoing risk stratification in determining the use of two- vs. three or more drug PEP regimens, (3) updated drug choices for PEP, (4) the safety and tolerability of

antiretroviral agents for the general population and pregnant or lactating HCP, and (5) any other topics in the 2005 guideline needed to be updated.

At the July 2011meeting, a CDC representative presented a review of the 2005 guideline recommendations, surveillance data on occupational exposures from the National Surveillance System for Healthcare Workers (NaSH),(12) and data from the National Clinicians Postexposure Prophylaxis Hotline (PEPline) on the numbers of occupational exposures to HIV managed annually, PEP regimens recommended, and challenges experienced with implementation of the 2005 guidelines. An FDA representative presented a review of the new medications that have become available since 2005 for the treatment of HIV-infected individuals, information about medication tolerability and toxicity, and the use of these medications during pregnancy. These presentations were followed by a discussion of the topics listed above.

Among the challenges discussed regarding implementation of the 2005 guidelines were the difficulties in determining level of risk of HIV transmission for individual exposure incidents which in turn determined the number of drugs recommended for HIV PEP. The consensus of the meeting participants^* was no longer to recommend exposure risk stratification (discussed in detail in the "Recommendations for the Selection of Drugs for HIV PEP" section of the guideline below). To update the drug choices for PEP, all drugs available for the treatment of HIV infected individuals were discussed with regards to tolerability, side effects, toxicity, safety in pregnancy and lactation, pills burden, and frequency of dosing. A hierarchy of recommended drugs/regimens was developed at the meeting and utilized in creating the PEP regimen recommendations (Appendices A and B) in these guidelines. Among other topics identified as needing an update were the acceptable HIV testing platforms available for source patient and

follow-up testing of exposed HCP, the timing of such testing, depending on the platform used, and the potential utility of source patient drug-resistance information/testing in PEP regimens.

After the expert consultation, the expert panelists received draft copies of these guidelines as they were updated and provided insights, information, suggestions, and edits, and participated in subsequent teleconferences with the PHS working group, to assist in developing these recommendations. Proposed recommendation updates were presented to the Healthcare Infection Control Practices Advisory Committee in November 2011(13) and June 2012(14) during public meetings. The PHS working group considered all available information, expert opinion, and feedback in finalizing the recommendations in this update.

Definition of Health-Care Personnel and Exposure

The definitions of HCP and occupational exposures are unchanged from those used in 2001 and 2005.(5, 6) The term HCP refers to all paid and unpaid persons working in healthcare settings who have the potential for exposure to infectious materials including body substances (e.g., blood, tissue, and specific body fluids), contaminated medical supplies and equipment, or contaminated environmental surfaces. HCP might include, but are not limited to, emergency medical service personnel, dental personnel, laboratory personnel, autopsy personnel, nurses, nursing assistants, physicians, technicians, therapists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care but potentially exposed to blood and body fluids (e.g., clerical, dietary, housekeeping, security, maintenance, and volunteer personnel). The same principles of exposure management could be applied to other workers with potential for occupational exposure to blood and body fluids in other settings.

An exposure that might place HCP at risk for HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious. In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious. Although semen and vaginal secretions have been implicated in the sexual transmission of HIV, they have not been implicated in occupational transmission from patients to HCP. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission of HIV infection from these fluids is unknown; the potential risk to HCP from occupational exposures has not been assessed by epidemiologic studies in healthcare settings. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they are visibly bloody.(11)

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection by this route has been reported rarely, but not after an occupational exposure.(15-20)

Risk for Occupational Transmission of HIV

Factors associated with risk for occupational transmission of HIV have been described; risks vary with the type and severity of exposure.(4, 5, 11) In prospective studies of HCP, the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood has been

estimated to be approximately 0.3% (95% confidence interval [CI] = 0.2%--0.5%)(11) and after a mucous membrane exposure, approximately 0.09% (CI = 0.006%--0.5%).(21) Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures.

Epidemiologic and laboratory studies suggest that multiple factors might affect the risk for HIV transmission after an occupational exposure.(22) In a retrospective case-control study of HCP who had percutaneous exposure to HIV, increased risk for HIV infection was associated with exposure to a larger quantity of blood from the source person as indicated by 1) a device (e.g., a needle) visibly contaminated with the patient's blood, 2) a procedure that involved a needle being placed directly in a vein or artery, or 3) a deep injury. The risk also was increased for exposure to blood from source persons with terminal illness, likely reflecting the higher titer of HIV in blood late in the course of acquired immunodeficiency syndrome (AIDS) Taken together, these factors suggest a direct inoculum effect (i.e., the larger the viral inoculum, the higher the risk for infection). One laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles lends further credence to the observed variation in risk related to inoculum size.(23)

Exposure to a source patient with an undetectable serum viral load does not eliminate the possibility of HIV transmission or the need for PEP and follow-up testing. While the risk of transmission from an occupational exposure to a source patient with an undetectable serum viral

load is thought to be very low, PEP should still be offered. Plasma viral load (e.g., HIV RNA) reflects only the level of cell-free virus in the peripheral blood; persistence of HIV in latently infected cells, despite patient treatment with antiretroviral drugs, has been demonstrated,(24, 25) and such cells might transmit infection even in the absence of viremia. HIV transmission from exposure to a source person who had an undetectable viral load has been described in cases of sexual and mother-to-child transmissions.(26, 27)

Antiretroviral Agents for PEP

Antiretroviral agents from six classes of drugs are currently available to treat HIV infection.(28) These include the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), an integrase strand transfer inhibitor (INSTI), and a chemokine (C-C motif) receptor 5 (CCR5) antagonist. Only antiretroviral agents approved by FDA for treatment of HIV infection are included in these guidelines, though none of these agents has an FDA-approved indication for administration as PEP. The rationale for offering antiretroviral medications as HIV PEP is based upon our current understanding of the pathogenesis of HIV infection and the plausibility of pharmacologic intervention in this process, studies of the efficacy of antiretroviral chemoprophylaxis in animal models,(29, 30) and epidemiologic data from HIV-exposed HCP.(22, 31) The recommendations in this report provide guidance for PEP regimens comprised of three (or when appropriate, more) antiretrovirals, consonant with currently recommended treatment guidelines for HIV infected individuals.(28)

Toxicity and Drug Interactions of Antiretroviral Agents

Persons receiving PEP should complete a full 4-week regimen.(5) However, previous results show a substantial proportion of HCP taking an earlier generation of antiretroviral agents as PEP frequently reported side effects,(12, 32-40) and many were unable to complete a full 4-week course of HIV PEP due to these effects and toxicities.(32-37) Because all antiretroviral agents have been associated with side effects (Appendix B),(28) the toxicity profile of these agents, including the frequency, severity, duration, and reversibility of side effects, is a critical consideration in selection of an HIV PEP regimen. The majority of data concerning adverse events have been reported primarily for persons with established HIV infection receiving prolonged antiretroviral therapy and therefore might not reflect the experience of uninfected persons who take PEP. In fact, anecdotal evidence from clinicians knowledgeable about HIV treatment indicates that antiretroviral agents are tolerated more poorly by HCP taking HIV PEP than by HIV-infected patients on antiretroviral medications. As side effects have been cited as a major reason for not completing PEP regimens as prescribed, the selection of regimens should be heavily influenced toward those that are best tolerated by HCP receiving PEP. Potential side effects of antiretroviral agents should be discussed with the PEP recipient, and, when anticipated, preemptive prescribing of agents for ameliorating side effects (e.g. anti-emetics, anti-spasmodics, etc.) may improve PEP regimen adherence.

In addition, the majority of approved antiretroviral agents might have potentially serious drug interactions when used with certain other drugs, thereby requiring careful evaluation of concomitant medications, including over-the-counter medications and supplements (e.g., herbals), used by an exposed person before prescribing PEP and close monitoring for toxicity of

anyone receiving these drugs.(28) PIs and NNRTIs have the greatest potential for interactions with other drugs. Information regarding potential drug interactions has been published and up-to-date information can be found in the *Guidelines for the use of antiretroviral agents in HIV-1 infected-adults and adolescents.*(28) Additional information is included in the manufacturers' package inserts. Consultation with a pharmacist or physician who is an expert in HIV PEP and antiretroviral medication drug interactions is strongly encouraged.

Selection of HIV PEP Regimens

Guidelines for treating HIV infection, a condition typically involving a high total body burden of HIV, recommend use of three or more drugs. Although the applicability of these recommendations to PEP is unknown, newer antiretroviral agents are better tolerated and have preferable toxicity profiles than agents previously used for PEP.(28) As less toxic and better tolerated medications for the treatment of HIV infection are now available, minimizing the risk of PEP noncompletion, and the optimal number of medications needed for HIV PEP remains unknown, the U.S. Public Health Services Working Group recommends prescribing three (or more) tolerable drugs as PEP for all occupational exposures to HIV. Medications included in an HIV PEP regimen should be selected to optimize side effect and toxicity profiles and a convenient dosing schedule to encourage HCP completion of the PEP regimen.

Resistance to Antiretroviral Agents

Known or suspected resistance of the source virus to antiretroviral agents, particularly to one or more of those that might be included in a PEP regimen, raises concerns about reduced PEP efficacy.(41) Drug resistance to all available antiretroviral agents has been reported, and cross-

resistance within drug classes occurs frequently.(42) Occupational transmission of drug-resistant HIV strains, despite PEP with combination drug regimens, has been reported.(43-45) If a source patient is known to harbor drug-resistant HIV, expert consultation is recommended for selection of an optimal PEP regimen. However awaiting expert consultation should not delay the initiation of HIV PEP. In instances of an occupational exposure to drug-resistant HIV, administration of antiretroviral agents to which the source patient's virus is unlikely to be resistant is recommended for PEP.

Information on whether a source patient harbors drug-resistant HIV may be unclear or unavailable at the time of an occupational exposure. Resistance should be suspected in a source patient who experiences clinical progression of disease, a persistently increasing viral load, or decline in CD4+ T-cell count despite therapy, or in instances in which a virologic response to therapy fails to occur. However, resistance testing of the source virus at the time of an exposure is impractical because the results will not be available in time to influence the choice of the initial PEP regimen. If, in the management of an occupational exposure to HIV, source patient HIV drug resistance is suspected, consultation with an expert in HIV management is recommended so that antiretroviral agents to which the source patients virus is unlikely to be resistant may be identified and prescribed. However, awaiting expert consultation should, again, not delay initiation of HIV PEP. If drug resistance information becomes available later in a course of PEP, this information should be discussed with the expert consultant for possible modification of the PEP regimen.

Antiretroviral Drugs During Pregnancy and Lactation

The decision to offer HIV PEP to a pregnant or breastfeeding healthcare provider should be based upon the same considerations that apply to any provider who sustains an occupational exposure to HIV. The risk of HIV transmission poses not only a threat to the mother, but also to the fetus and infant, as the risk of mother-to-child HIV transmission is markedly increased during acute HIV infection during pregnancy and breastfeeding.(46) However, unique considerations are associated with the administration of antiretroviral agents to pregnant HCP, and the decision to use antiretroviral drugs during pregnancy should involve both counseling and discussion between the pregnant woman and her healthcare provider(s) regarding the potential risks and benefits of PEP for both the healthcare provider and for her fetus.

The potential risks associated with antiretroviral drug exposure for pregnant women, fetuses and infants depend on the duration of exposure as well as the number and type of drugs. Information about the use of newer antiretroviral agents, administered as PEP to HIV-uninfected pregnant women, is limited. For reasons including the complexities associated with appropriate counseling about the risks and benefits of PEP, as well as the selection of antiretroviral drugs in pregnant women, expert consultation should be sought in all cases in which antiretroviral medications are prescribed to pregnant HCP for PEP.

In general, antiretroviral drug toxicity has not been shown to be increased in pregnancy. Conflicting data have been published concerning the risk of preterm delivery in pregnant women receiving antiretroviral drugs, particularly protease inhibitors;(47) in studies that have reported a positive association, the increase in risk was primarily observed in women who were receiving antiretroviral drug regimens at the time of conception and continued during pregnancy. Fatal(48)

and nonfatal(49) lactic acidosis has been reported in pregnant women treated throughout gestation with a combination of d4T and ddI. Prescribing this drug combination for PEP is not recommended. Physiologic changes that occur during pregnancy may alter antiretroviral drug metabolism, and, therefore, optimal drug dosing. The clinical significance of these changes is not clear, particularly when used for PEP in HIV-uninfected women. For details on antiretroviral drug choice and dosing in pregnancy, see *Recommendations for use of Antiretroviral drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.*(10)

Prospective data from the Antiretroviral Pregnancy Registry do not demonstrate an increase in overall birth defects associated with first trimester antiretroviral drug use. In this population, the birth defect prevalence is 2.9 per 100 live births, similar to the prevalence in the general population in the CDC's birth defect surveillance system (i.e., 2.7 per 100 live births).(50) Central nervous system defects were observed in fetal primates that experienced *in utero* efavirenz (EFV) exposure and that had drug levels similar to those representing human therapeutic exposure; however, the relevance of *in vitro* laboratory and animal data to humans is unknown.(10) While human data are reassuring,(51) one case of meningomyelocele has been reported among the Antiretroviral Pregnancy Registry prospective cases and data are insufficient to conclude that there is no increase in a rare outcome such as neural tube defect with first trimester EFV exposure.(50) For these reasons, we recommend that pregnant women not use EFV during the first trimester.(10) If EFV-based PEP is used in women, a pregnancy test should be done to rule out early pregnancy, and non-pregnant women who are receiving EFV-based PEP should be counseled to avoid pregnancy until after PEP is completed. HCP who care for women who receive antiretroviral drugs during pregnancy are strongly advised to report

instances of prenatal exposure to the Antiretroviral Pregnancy Registry (http://www.APRegistry.com). The currently available literature contains only limited data describing the long-term effects (e.g., neoplasia, mitochondrial toxicity) of *in utero* antiretroviral drug exposure. For this reason, long-term follow-up is recommended for all children who experienced *in utero* exposures.(10, 52, 53)

Antiretroviral drug levels in breast milk vary among drugs, with administration of some drugs resulting in high levels (e.g., lamivudine) while other drugs, such as protease inhibitors and tenofovir, are associated with only limited penetration into milk.(54, 55) Administration of antiretroviral triple drug regimens to breastfeeding HIV-infected women has been shown to decrease the risk of transmission to their infants and infant toxicity has been minimal. Prolonged maternal antiretroviral drug use during breastfeeding may be associated with increased infant hematologic toxicity,(56, 57) but limited drug exposure during 4 weeks of PEP may also limit the risk of drug toxicity to the breastfeeding infant. Breastfeeding should not be a contraindication to use of PEP when needed, given the high risk of mother-to-infant transmission with acute HIV infection during breastfeeding.(46) The lactating healthcare provider should be counseled regarding the high risk of HIV transmission through breast milk should acute HIV infection occur (in a study in Zimbabwe, the risk of breast milk HIV transmission in the 3 months after seroconversion was 77.6 infections/100 child-years).(58) To completely eliminate any risk of HIV transmission to her infant, the provider may want to consider stopping breastfeeding. Ultimately, lactating women with occupational exposures to HIV who will take antiretroviral medications as PEP must be counseled to weigh the risks and benefits of continued breastfeeding both while taking PEP, and while being monitored for HIV seroconversion.

Management of Occupational Exposure by Emergency Physicians

Many HCP exposures to HIV occur outside of occupational health clinic hours of operation, or at sites at which occupational health services are unavailable, and initial exposure management is often overseen by emergency physicians or other providers who are not experts in the treatment of HIV infection or the use of antiretroviral medications. These providers may not be familiar with either the PHS guidelines for the management of occupational exposures to HIV or with the available antiretroviral agents and their relative risks and benefits. Previous focus groups conducted among emergency department physicians who had managed occupational exposures to blood and body fluids in 2002(59) identified three challenges in occupational exposure management: evaluation of an unknown source patient or a source patient who refused testing, inexperience in managing occupational HIV exposures, and counseling of exposed workers in busy EDs. For these reasons, the U.S. Public Health Services Working Group recommends that institutions develop clear protocols for the management of occupational exposures to HIV, indicating a formal expert consultation (e.g. the in-house infectious diseases consultant, PEPline, etc.) mechanism, appropriate initial source patient and exposed provider laboratory testing, procedures for counseling the exposed provider, identifying and having an initial HIV PEP regimen available, and a mechanism for outpatient HCP follow-up. In addition, these protocols must be distributed appropriately and must be readily available (e.g. posted on signs in the emergency department, posted on a website, disseminated to staff on pocket-sized cards, etc.) to emergency physicians and any other providers who may be called upon to manage these exposure incidents.

Recommendations for the Management of HCP Potentially Exposed to HIV

Exposure prevention remains the primary strategy for reducing occupational bloodborne pathogen infections. However, when occupational exposures do occur, PEP remains an important element of exposure management.

HIV PEP

The recommendations provided in this report apply to situations in which a healthcare provider has been exposed to a source person who either has, or there is a reasonable suspicion of, HIV infection. These recommendations reflect expert opinion and are based on limited data regarding safety, tolerability, efficacy, and toxicity of PEP. If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued and no further HIV follow-up testing is indicated for the exposed provider. Because the great majority of occupational HIV exposures do not result in transmission of HIV, the potential benefits and risks of PEP (including the potential for severe toxicity and drug interactions, such as may occur with oral contraceptives, H_2-receptor antagonists, and proton pump inhibitors, among many other agents) must be considered carefully when prescribing PEP. HIV PEP medication regimen recommendations are listed in Appendix A, and more detailed information on individual antiretroviral medications is provided in Appendix B. Because of the complexity of selecting HIV PEP regimens, whenever possible, these recommendations should be implemented in consultation with persons who have expertise in the administration of antiretroviral therapy and who are knowledgeable about HIV transmission. Reevaluation of exposed HCP is recommended within 72 hours post-exposure, especially, as additional information about the exposure or source person becomes available.

Source Patient HIV Testing

Whenever possible, the HIV status of the exposure source patient should be determined to guide appropriate use of HIV PEP. Although concerns have been expressed about HIV-negative sources that might be in the so-called "window period" before seroconversion (i.e., the period of time between initial HIV infection and the development of detectable HIV antibodies), to date, no such instances of occupational transmission have been detected in the United States. Hence, investigation of whether a source patient might be in the "window period" is unnecessary for determining whether HIV PEP is indicated unless acute retroviral syndrome is clinically suspected. Rapid HIV testing of source patients facilitates timely decision-making regarding the need for administration of HIV PEP after occupational exposures to sources whose HIV status is unknown. FDA-approved rapid tests can produce HIV test results within 30 minutes, with sensitivities and specificities similar to those of first and second generation enzyme immunoassays (EIAs).(60) Third generation chemiluminescent immunoassays, run on automated platforms, can detect HIV specific antibodies two weeks sooner than conventional EIAs(60) and generate test results in an hour or less.(61) Fourth-generation combination p24 antigen-HIV antibody (Ag/Ab) tests produce both rapid and accurate results, and their p24 antigen detection allows identification of most infections during the "window period".(62) Rapid determination of source patient HIV status provides essential information about the need to initiate and/or continue PEP. Regardless of which type of HIV testing is employed, all of the above tests are acceptable for determination of source patient HIV status. Administration of PEP should not be delayed while waiting for test results. If the source patient is determined to be HIV-negative, PEP should be discontinued and no follow-up HIV testing for the exposed provider is indicated.

Timing and Duration of PEP

Animal studies have suggested that PEP is most effective when begun as soon as possible after the exposure and that PEP becomes less effective as time from the exposure increases,(29, 30) PEP should be initiated as soon as possible, preferably within hours of exposure. Occupational exposures to HIV should be considered urgent medical concerns and treated immediately. For example, a surgeon who sustains an occupational exposure to HIV while performing a surgical procedure should promptly scrub out of the surgical case, if possible, and seek immediate medical evaluation for the injury and PEP. Additionally, if the HIV status of a source patient for whom the practitioner has a reasonable suspicion of HIV infection is unknown and the practitioner anticipates that hours or days may be required to resolve this issue, antiretroviral medications should be started immediately rather than delayed.

Although animal studies demonstrate that PEP is likely to be less effective when started more than 72 hours postexposure,(30, 63) the interval after which no benefit is gained from PEP for humans is undefined. If initiation of PEP is delayed, the likelihood increases that benefit might not outweigh the risks inherent in taking antiretroviral medications. Initiating therapy after a longer interval (e.g., 1 week) might still be considered for exposures that represent an extremely high risk for transmission. The optimal duration of PEP is unknown; however, duration of treatment has been shown to influence success of PEP in animal models.(30) Because 4 weeks of PEP appeared protective in *in vitro*, animal(29, 30, 63, 64) and occupational(22) studies, PEP should be administered for 4 weeks, if tolerated.

Recommendations for the Selection of Drugs for HIV PEP

PHS no longer recommends that the severity of exposure be used to determine the number of drugs to be offered in an HIV PEP regimen, and a regimen containing three (or more) antiretroviral drugs is now recommended routinely for all occupational exposures to HIV. Examples of recommended PEP regimens include those consisting of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone plus an integrase strand transfer inhibitor (INSTI), a protease inhibitor (boosted with ritonavir), or a non-nucleoside reverse transcriptase inhibitor. Other antiretroviral drug combinations may be indicated for specific cases (e.g. an exposure to a source patient harboring drug-resistant HIV), but should only be prescribed after consultation with an expert in the use of antiretroviral agents. No new definitive data exist to demonstrate increased efficacy of three-drug HIV PEP regimens, compared with the previously recommended two-drug HIV PEP regimens for occupational HIV exposures associated with a lower level of transmission risk. The recommendation for consistent use of three-drug HIV PEP regimens reflects (1) studies demonstrating superior effectiveness of three drugs in reducing viral burden in HIV-infected persons when compared with two agents,(28, 65, 66) (2) concerns about source patient drug-resistance to agents commonly used for PEP,(67, 68) (3) the safety and tolerability of new HIV drugs, and (4) the potential for improved PEP regimen adherence due to newer medications that are likely to have fewer side effects. Clinicians facing challenges such as antiretroviral medication availability, potential adherence and toxicity issues, or others associated with a three-drug PEP regimen, might still consider a two-drug PEP regimen in consultation with an expert.

The drug regimen selected for HIV PEP should have a favorable side effect profile as well as a convenient dosing schedule to facilitate both adherence to the regimen and completion of 4 weeks of PEP. Because the agents administered for PEP still can be associated with severe side effects, PEP is not justified for exposures that pose a negligible risk for transmission. Expert consultation could be helpful in determining whether an exposure constitutes a risk that would warrant PEP. The preferred HIV PEP regimen recommended in this guideline should be reevaluated and modified whenever additional information is obtained concerning the source of the occupational exposure (e.g., possible treatment history or antiretroviral drug resistance), or if expert consultants recommend the modification. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended. Such consultation should not, however, delay timely initiation of PEP.

PHS now recommends emtricitabine (FTC) plus tenofovir (TDF) (these two agents may be dispensed as Truvada®, a fixed-dose combination tablet) plus raltegravir (RAL) as HIV PEP for occupational exposures to HIV. This regimen is tolerable, potent, conveniently administered, and has been associated with minimal drug interactions. Additionally, although we have only limited data on the safety of RAL during pregnancy, this regimen could be administered to pregnant HCP as PEP (see discussion above). Preparation of this PEP regimen in single dose "starter packets," which are kept on-hand at sites expected to manage occupational exposures to HIV, may facilitate timely initiation of PEP.

Several drugs may be used as alternatives to FTC plus TDF plus RAL. TDF has been associated with renal toxicity,(69) and an alternative should be sought in HCP who have underlying renal

disease. Zidovudine (ZDV) could be used as an alternative to TDF and could be conveniently prescribed in combination with lamivudine (3TC), to replace both TDF and FTC, as Combivir®. Alternatives to RAL include darunavir (DRV) plus ritonavir (RTV), etravirine (ETV), rilpivirine (RPV), atazanavir (ATV) plus RTV, and lopinivir (LPV) plus RTV. When a more cost-efficient alternative to RAL is required, saquinivir (SQV) plus RTV could be considered. A list of preferred alternative PEP regimens is provided in Appendix A.

Some antiretroviral drugs are contraindicated as HIV PEP or should only be used for PEP under the guidance of expert consultants (Appendix A and B). Among these drugs are nevirapine (NVP), which should not be used and is contraindicated as PEP because of serious reported toxicities, including hepatotoxicty (with one instance of fulminant liver failure requiring liver transplantation), rhabdomyolysis, and hypersensitivity syndrome.(70-72) Antiretroviral drugs not routinely recommended for use as PEP because of the higher risk for potentially serious or life-threatening adverse events, include ddI and tipranavir (TPV). The combination of ddI and d4T should not be prescribed as PEP due to increased risk of toxicity (e.g., peripheral neuropathy, pancreatitis, and lactic acidosis). Additionally, abacavir (ABC) should only be used as HIV PEP in the setting of expert consultation, due to the need for prior HLA B57-01 testing to identify individuals at higher risk for a potentially fatal hypersensitivity reaction.(28) The fusion inhibitor, enfuvirtide (Fuzeon™, T20), is also not generally recommended as PEP, unless its use is deemed necessary during expert consultation, due to its subcutaneous route of administration, significant side effects, and potential for development of anti-T20 antibodies that may cause false-positive HIV antibody tests among uninfected patients.

When the source patient's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended; again, expert consultation is strongly advised. If this information is not immediately available, the initiation of PEP, if indicated, should not be delayed; the regimen can be modified after PEP has been initiated, whenever such modifications are deemed appropriate. For HCP who initiate PEP, re-evaluation of the exposed person should occur within 72 hours postexposure, especially if additional information about the exposure or source person becomes available.

Regular consultation with experts in antiretroviral therapy and HIV transmission is strongly recommended. Preferably, a process for involvement of an expert consultant should be formalized in advance of an exposure incident. Certain institutions have required consultation with a hospital epidemiologist or infectious diseases consultant when HIV PEP use is under consideration. At a minimum, expert consultation is recommended for the situations described in Box 1.

Resources for consultation are available from the following sources:

- PEPline at http://www.nccc.ucsf.edu/about_nccc/pepline/; telephone 888-448-4911;
- HIV Antiretroviral Pregnancy Registry at http://www.apregistry.com/index.htm ; Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405. Telephone: 800-258-4263; Fax: 800-800-1052; E-mail: registies@Kendle.com;
- FDA (for reporting unusual or severe toxicity to antiretroviral agents) at http://www.fda.gov/medwatch; telephone: 800-332-1088; address: MedWatch, The FDA

Safety Information and Adverse Event Reporting Program, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852;

- CDC's "Cases of Public Health Importance" (COPHI) coordinator (for reporting HIV infections in HCP and failures of PEP) at telephone 404-639-2050
- HIV/AIDS Treatment Information Service at http://aidsinfo.nih.gov.

Follow-Up of Exposed HCP

Importance of Follow-up Appointments

HCP who have experienced occupational exposure to HIV should receive follow-up counseling, postexposure testing, and medical evaluation regardless of whether they take PEP. Greater emphasis is placed upon the importance of follow-up of HCP on HIV PEP within 72 hours of exposure and improving follow-up care provided to exposed HCP (Box 2). Careful attention to follow-up evaluation within 72 hours of exposure can: 1) provide another (and perhaps less anxiety-ridden) opportunity to allow the exposed HCP to ask questions and for the counselor to make certain that the exposed HCP has a clear understanding of the risks for infection and the risks and benefits of PEP, 2) ensure that continued treatment with PEP is indicated, 3) increase adherence to HIV PEP regimens, 4) manage associated symptoms and side-effects more effectively, 5) provide an early opportunity for ancillary medications or regimen changes, 6) improve detection of serious adverse effects, and 7) improve the likelihood of follow-up serologic testing for a larger proportion of exposed personnel to detect infection. Closer follow-up should in turn reassure HCP who become anxious after these events.(73, 74) The psychological impact of needlesticks or exposure to blood or body fluid should not be underestimated for HCP. Exposed personnel should be advised to use precautions (e.g., use of

barrier contraception, avoid blood or tissue donations, pregnancy, and if possible, breastfeeding) to prevent secondary transmission, especially during the first 6-12 weeks postexposure. Providing HCP with psychological counseling should be an essential component of the management and care of exposed HCP.

Postexposure Testing

HIV testing should be used to monitor HCP for seroconversion after occupational HIV exposure. After baseline testing at the time of exposure, follow-up testing should be performed at 6 weeks, 12 weeks, and 6 months after exposure. Use of fourth generation HIV Ag/Ab combination immunoassays allow for earlier detection of HIV infection.(60, 62, 75) If a provider is certain that a fourth generation combination HIV Ag/Ab test is used, HIV follow-up testing could be concluded earlier than 6 months after exposure. In this instance, an alternative follow-up testing schedule could be used (e.g., baseline testing, 6 weeks, and then concluded at 4 months after the exposure). Extended HIV follow-up (e.g., for 12 months) is recommended for HCP who become infected with HCV after exposure to a source who is co-infected with HIV and HCV. Whether extended follow-up is indicated in other circumstances (e.g., exposure to a source co-infected with HIV and HCV in the absence of HCV seroconversion or for exposed persons with a medical history suggesting an impaired ability to mount an antibody response to acute infection) is unknown. Although rare instances of delayed HIV seroconversion have been reported,(76, 77) adding to an exposed persons' anxiety by routinely extending the duration of postexposure follow-up is not warranted. However, decisions to extend follow-up in a particular situation should be based on the clinical judgment of the exposed person's health-care provider and should not be precluded because of HCP anxiety. HIV tests should also be performed on any exposed

person who has an illness compatible with an acute retroviral syndrome, regardless of the interval since exposure. A person in whom HIV infection is identified should be referred to a specialist who has expertise in HIV treatment and counseling for medical management. Health-care providers caring for persons who have occupationally acquired HIV infection should report these cases to their state health departments and to CDC's COPHI coordinator at telephone 404-639-2050.

Monitoring and Management of PEP Toxicity

If PEP is used, HCP should be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. In addition, HCP taking antiretrovirals should be evaluated if any acute symptoms develop while on therapy. The scope of testing should be based on medical conditions in the exposed person and the known and anticipated toxicities of the drugs included in the PEP regimen. Minimally, laboratory monitoring for toxicity should include a complete blood count and renal and hepatic function tests. If toxicities are identified, modification of the regimen should be considered after expert consultation. In addition, depending on the clinical situation, further diagnostic studies may be indicated (e.g., monitoring for hyperglycemia in a diabetic whose regimen includes a PI).

Exposed HCP who choose to take PEP should be advised of the importance of completing the prescribed regimen. Information should be provided about: potential drug interactions and prescription/nonprescription drugs and nutritional supplements that should not be taken with PEP or require dose or administration adjustments, side effects of prescribed drugs, measures (including pharmacological interventions) that may assist in minimizing side effects, and methods of clinical monitoring for toxicity during the follow-up period. HCP should be advised

that evaluation of certain symptoms (e.g., rash, fever, back or abdominal pain, pain on urination or blood in the urine, dark urine, yellowing of the skin or whites of the eyes, or symptoms of hyperglycemia (e.g., increased thirst or frequent urination) should not be delayed. Serious adverse events[§] should be reported to FDA's MedWatch program.

Reevaluation and Updating of HIV PEP Guidelines

As new antiretroviral agents for treatment of HIV infection and additional information concerning early HIV infection and prevention of HIV transmission become available, the PHS Interagency Working Group will assess the need to update these guidelines. Updates will be published periodically as appropriate.

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Competing Interests

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Information included in these recommendations might not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standard for product approval.

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BOX 1. Situations for Which Expert Consultation for Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) is Recommended

Delayed (i.e., later than 72 hours) exposure report
- Interval after which benefits from PEP are undefined

Unknown source (e.g., needle in sharps disposal container or laundry)
- Use of PEP to be decided on a case-by-case basis
- Consider severity of exposure and epidemiologic likelihood of HIV exposure
- Do not test needles or other sharp instruments for HIV

Known or suspected pregnancy in the exposed person
- Provision of PEP should not be delayed while awaiting expert consultation

Breastfeeding in the exposed person
- Provision of PEP should not be delayed while awaiting expert consultation

Known or suspected resistance of the source virus to antiretroviral agents
- If source person's virus is known or suspected to be resistant to one or more of the drugs considered for PEP, selection of drugs to which the source person's virus is unlikely to be resistant recommended
- Do not delay initiation of PEP while awaiting any results of resistance testing of the source person's virus

Toxicity of the initial PEP regimen
- Symptoms (e.g. GI symptoms and others) often manageable without changing PEP regimen by prescribing antimotility or antiemetic agents
- Counseling and support for management of side effects is very important as symptoms are often exacerbated by anxiety.

Serious medical illness in the exposed person
- Significant underlying illness (e.g. renal disease) or an exposed provider already taking multiple medications may increase the risk of drug toxicity and drug-drug interactions

Expert consultation can be made with local experts or by calling the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911.

BOX 2. Follow-Up of Health-Care Personnel (HCP) Exposed to Known or Suspected Human Immunodeficiency Virus (HIV)-Positive Sources

Counseling (At the time of exposure, and at follow-up appointments) Exposed HCP should be advised to use precautions (e.g., use of barrier contraception, avoid blood or tissue donations, pregnancy, and if possible, breastfeeding) to prevent secondary transmission, especially during the first 6–12 weeks postexposure.

For exposures for which PEP is prescribed, HCP should be informed regarding:

- possible drug toxicities (e.g. rash and hypersensitivity reactions which could imitate acute HIV seroconversion and the need for monitoring)
- possible drug interactions, and
- the need for adherence to PEP regimens.

Early Reevaluation after Exposure Regardless of whether a healthcare provider is taking PEP, reevaluation of exposed HCP within 72 hours after exposure is strongly recommended, as additional information about the exposure or source person may be available

Follow-up Testing and Appointments Follow-up testing at a minimum should include:

- HIV testing at baseline, 6 weeks, 12 weeks, and 6 months postexposure; Alternatively, if the clinician is certain that a 4th generation combination HIV p24 antigen-HIV antibody test is being utilized, then HIV testing could be performed at baseline, 6 weeks, and concluded at 4 months postexposure.
- Complete Blood counts, Renal and Hepatic Function Tests (At baseline and 2 weeks postexposure; further testing may be indicated if abnormalities were detected)

HIV testing results should preferably be given to the exposed healthcare provider at face to face appointments

APPENDIX A: HIV Postexposure Prophylaxis Regimens

PREFERRED HIV PEP REGIMEN
Raltegravir (Isentress®; RAL) 400mg PO Twice Daily Plus Truvada™,1 PO Once Daily [Tenofovir DF (Viread®; TDF) 300mg + emtricitabine (Emtriva™; FTC) 200mg]

ALTERNATIVE REGIMENS **(May combine one drug or drug pair from the left column with 1 pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column. Prescribers unfamiliar with these agents/regimens should consult physicians familiar with the agents and their toxicities.)*^**	
Raltegravir (Isentress®; RAL)	Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™
Darunavir (Prezista®; DRV) + ritonavir (Norvir®; RTV)	Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)
Etravirine (Intelence®; ETR)	Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir®
Rilpivirine (Edurant™; RPV)	Zidovudine (Retrovir®; ZDV; AZT) + emtricitabine (Emtriva™; FTC)
Atazanavir (Reyataz®; ATV) + ritonavir (Norvir®; RTV)	
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	
The following alternative is a complete fixed-dose combination regimen and no additional antiretrovirals are needed: Stribild™ (elvitegravir, cobicistat, tenofovir DF, emtricitabine)	

ALTERNATIVE ANTIRETROVIRAL AGENTS FOR USE AS PEP <u>ONLY</u> WITH EXPERT CONSULTATION^
Abacavir (Ziagen®; ABC)
Efavirenz (Sustiva®; EFV)
Enfuvirtide (Fuzeon™; T20)
Fosamprenavir (Lexiva®; FOSAPV)
Maraviroc (Selzentry®; MVC)
Saquinavir (Invirase®; SQV)
Stavudine (Zerit®; d4T)

ANTIRETROVIRAL AGENTS GENERALLY NOT RECOMMENDED FOR USE AS PEP
Didanosine (Videx EC®; ddI)
Nelfinavir (Viracept®; NFV)
Tipranavir (Aptivus®; TPV)

ANTIRETROVIRAL AGENTS CONTRAINDICATED AS PEP
Nevirapine (Viramune®; NVP)

--- For consultation or assistance with HIV PEP, contact PEPline at telephone 888-448-4911 or visit their website http://www.nccc.ucsf.edu/about_nccc/pepline/. DF, disoproxil fumarate; PO, per os.

*The alternatives regimens are listed in order of preference, however, other alternatives may be reasonable based upon patient and clinician preference.

^For Drug Dosing Information, see Appendix B

APPENDIX B:
Information on HIV Postexposure Prophylaxis Medications*^

Drug Name	Drug Class	Dosing (Dosage Form)	Advantages	Disadvantages
Abacavir (Ziagen®; ABC)	Nucleoside Reverse Transcriptase Inhibitor (NRTI)	ABC : 600 mg daily (available as a 300 mg tablet) Also available as component of fixed-dose combination Epzicom®, dosed daily (300mg 3TC + 600mg ABC) Trizivir®, dosed twice daily (150mg 3TC + 300mg ABC + 300mg AZT)	Take without regard for food	Potential for life-threatening ABC hypersensitivity reaction (rash, fever, nausea, vomiting, diarrhea, abdominal pain, malaise, respiratory symptoms) in patients with HLA-B*5701; requires patient testing prior to use which may not be available nor practical prior to initiating PEP
Atazanavir (Reyataz®; ATV)	Protease Inhibitor (PI)	ATV: 300 mg + RTV: 100 mg once daily (Preferred dosing for PEP^) ATV: 400 mg once daily without RTV (Alternative dosing-may not be used in combination with TDF) (available as 100, 150, 300, and 200 mg capsules)	Well tolerated	Indirect hyperbilirubinemia and jaundice common Skin rash Nephrolithiasis Potential for serious or life-threatening drug interactions that may affect dosing Absorption depends on low pH; Caution when coadministered with H2 Antagonists, antacids, and proton pump inhibitors PR interval prolongation

				Caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation Must be given with food
Darunavir (Prezista®; DRV)	PI	DRV: 800 mg once daily + RTV: 100 mg once daily (Preferred dosing for PEP^) DRV: 600 mg twice daily + RTV: 100 mg twice daily (Alternative dosing) (available as 75, 150, 400, and 600 mg tablets)	Well tolerated	Rash (DRV has sulfonamide moiety) Diarrhea, nausea, headache Hepatotoxicity Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food and with RTV
Efavirenz (Sustiva®; EFV)	Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	EFV: 600 mg daily (available as 50, 200 mg capsules and 600 mg tablets) Also available as component of fixed-dose combination Atripla®, dosed daily (200mg FTC + 300mg TDF + 600mg EFV)	Available as a complete regimen dosed once per day	Rash Neuropsychiatric side effects (e.g., dizziness, somnolence, insomnia, or abnormal dreaming) common; severe psychiatric symptoms possible (dosing before bedtime might minimize these side effects); use with caution in shift workers Do not use during pregnancy; Teratogen in

				nonhuman primates Potential for serious or life-threatening drug interactions that may affect dosing May cause false-positive results with some cannabinoid and benzodiazepine screening assays Take on an empty stomach
Elvitegravir (EVG)	Integrase Strand Transfer Inhibitor (INSTI)	Available as a component of fixed-dose combination Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC)	Well tolerated Available as a complete regimen dosed once per day	Diarrhea, nausea, headache Nephrotoxicity; should not be administered to individuals with acute or chronic kidney injury or those with eGFR<70 Cobicistat is a pharmacokinetic enhancer to increase EVG exposures, has no antiviral activity, but is a potent CYP3A inhibitor Potential for serious or life-threatening drug interactions Must be given with food
Emtricitabine (Emtriva™; FTC)	NRTI	200 mg once daily (available as 200 mg capsule) Also available as	Well tolerated Minimal toxicity Minimal drug	Rash perhaps more frequent than with 3TC Hyperpigmentatio

		component of fixed-dose combination Atripla®, dosed daily (200mg FTC + 300mg TDF + 600mg EFV) Complera™, dosed daily (25mg RPV+ 300mg TDF + 200mg FTC) Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC) Truvada™, dosed daily (200mg FTC + 300mg TDF)	interactions Take without regard for food	n/skin discoloration If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation
Enfuvirtide (Fuzeon™; T20)	Fusion Inhibitor (FI)	T20: 90 mg (1 ml) twice daily by subcutaneous injection (available as Single-dose vial, reconstituted to 90 mg/ml)		Local injection site reactions occur in almost 100% of patients Never studied among antiretroviral-naïve or HIV-negative patients False-positive EIA HIV antibody tests might result from formation of anti-T20 antibodies that cross-react with anti-gp41 antibodies Twice-daily injection
Etravirine (Intelence®; ETR)	NNRTI	200 mg twice daily (available as 100mg and 200mg tablets)	Well tolerated and has not had the same frequency of CNS side effects reported as EFV	Rash (including SJS) and hypersensitivity (sometimes with organ dysfunction, including hepatic failure) Nausea

				Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food
Fosamprenavir (Lexiva®; FOSAPV)	PI	FOSAPV: 1400 mg daily + RTV: 100 mg once daily (Preferred dosing for PEP) FOSAPV: 1400 mg twice daily without RTV (Alternative dosing) (available as 700 mg tablets)	Well tolerated	Diarrhea, nausea, vomiting, headache, skin rash (FOSAPV has sulfonamide moiety) Potential for serious or life-threatening drug interactions that may affect dosing Oral contraceptives decrease FOSAPV concentrations Take with food if given with RTV
Lamivudine (Epivir®; 3TC)	NRTI	3TC : 300 mg once daily (Preferred dosing for PEP) 3TC : 150 mg twice daily (Alternative dosing) (available as a 150 or 300 mg tablet) Also available as component of fixed-dose combination generic lamivudine/zidovudine, dosed twice daily (150mg 3TC + 300mg AZT) Combivir®, dosed twice daily (150mg 3TC + 300mg AZT) Epzicom®, dosed daily	Well tolerated Minimal toxicity Minimal drug interactions Take without regard for food	If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation

		(300mg 3TC + 600mg ABC) Trizivir®, dosed twice daily (150mg 3TC + 300mg ABC + 300mg AZT)		
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	PI	Kaletra®: 400/100 mg = 2 tablets twice daily (Preferred dosing for PEP) Kaletra®: 800/200 mg = 4 tablets once daily (Alternative dosing) (available as 200/50 mg tablets)	Take without regard to food	GI intolerance, nausea, vomiting, diarrhea are common PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect. Potential for serious or life-threatening drug interactions that may affect dosing
Maraviroc (Selzentry®; MVC)	CCR5 Coreceptor Antagonist	MVC: 300 mg twice daily (dose may need adjustment by expert consultant if on concomitant CYP3A inducers) (available as 150 and 300 mg tablets)	Well tolerated	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, orthostatic hypotension Hepatotoxicity which may present with an allergic reaction including rash. Requires HIV tropism testing of source virus before treatment to ensure CCR5 tropic virus and efficacy, which

				may not be available nor practical prior to initiating PEP Potential for serious or life-threatening drug interactions that may affect dosing Dose adjustments for MVC required when given with potent CYP3A inhibitors or inducers
Raltegravir (Isentress®; RAL)	INSTI	400 mg twice daily (available as 400 mg tablet)	Well tolerated Minimal drug interactions Take without regard for food	Insomnia, nausea, fatigue, headache, severe skin and hypersensitivity reactions have been reported
Rilpivirine (Edurant™; RPV)	NNRTI	25 mg once daily (available as 25mg tablets) Also available as component of fixed-dose combination Complera™, dosed daily (25mg RPV + 300mg TDF + 300mg FTC)	Well tolerated and fewer rashes and fewer discontinuations for CNS adverse effects compared to EFV Available as a complete regimen dosed once per day	Depression, insomnia, rash, hypersensitivity, headache Potential for serious or life-threatening drug interactions that may affect dosing Caution when coadministered with H2 antagonists and antacids Coadministration with proton pump inhibitors is contraindicated Use RPV with caution when coadministered with a drug having a known risk

				of torsades de pointes. Must be given with food
Saquinavir (Invirase®; SQV)	PI	SQV: 1,000 mg + RTV: 100 mg twice daily (Preferred dosing for PEP) (available as 500 mg tablets)	Well-tolerated, although GI events common	GI intolerance, nausea, diarrhea, headache Pretreatment ECG recommended SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block. PR and QT interval prolongations, torsades de pointes has been reported Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food
Stavudine (Zerit®; d4T)	NRTI	d4T : 40 mg twice daily if body weight is >60 kg d4T : 30 mg twice	Take without regard for food	GI side effects include diarrhea and nausea

		daily if body weight is <60 kg (available as 15, 20, 30, and 40 mg tablets)		Hepatotoxicity, neurologic symptoms (e.g. peripheral neuropathy), and pancreatitis
Tenofovir DF (Viread®; TDF)	NRTI	300 mg once daily (available as 300 mg tablet) Also available as component of fixed-dose combination Atripla®, dosed daily (200mg FTC+ 300mg TDF + 600mg EFV) Complera™, dosed daily (25mg RPV + 300mg TDF + 200mg FTC) Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC) Truvada™, dosed daily (200mg FTC + 300mg TDF)	Well tolerated Take without regard for food	Asthenia, headache, diarrhea, nausea, vomiting Nephrotoxicity If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation Drug interactions
Zidovudine (Retrovir®; ZDV; AZT)	NRTI	AZT : 300 mg twice daily (available as 100 mg capsule or 300 mg tablet) Also available as component of fixed-dose combination generic lamivudine/zidovudine, dosed twice daily (150mg 3TC + 300mg AZT) Combivir®, dosed twice daily (150mg 3TC + 300mg AZT) Trizivir®, dosed twice daily (150 mg 3TC +	Take without regard for food	Side effects (especially nausea, vomiting, headache, insomnia, and fatigue) common and might result in low adherence Anemia and neutropenia

		300mg ABC + 300mg AZT)		

*This Appendix does not provide comprehensive information on each individual drug. For detailed information, please refer to individual drug package inserts. AV, atrioventricular; CNS, central nervous system; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EIA, enzyme immunoassay; GI, gastrointestinal; SJS, Stevens-Johnson syndrome.

^Certain antiretroviral agents such as protease inhibitors have the option of once or twice daily dosing depending on treatment history and use with ritonavir. For PEP the selection of dosing and schedule is to optimize adherence while minimizing side-effects where possible. This table includes the preferred dosing schedule for each agent and in all cases, with the exception of Kaletra, the once daily regimen option is preferred for PEP. Twice daily administration of Kaletra is better tolerated with respect to GI toxicities compared to the once daily regimen. Alternative dosing and schedules may be appropriate for PEP in certain circumstances, and should preferably be prescribed by individuals experienced in the use of antiretroviral medications.

EXHIBIT 55

PPG-TAB B: AMPLIFICATION OF REQUIREMENTS FOR PERMANENT CHANGE OF STATION (PCS) PERSONNEL IN THE CENTCOM AOR; TO ACCOMPANY MOD THIRTEEN TO USCENTCOM INDIVIDUAL PROTECTION AND INDIVIDUAL/UNIT DEPLOYMENT POLICY

1. General. This PPG-TAB B accompanies MOD THIRTEEN and provides amplification of the minimal requirements for PCS personnel in the CENTCOM Area of responsibility (AOR), including a list of medical conditions (paragraph 3 below) that may be sufficient to deny medical clearance for, or to disapprove PCS of, a Service Member, civilian employee, or uniformed embassy personnel (hereby referred to as 'personnel") assigned to CENTCOM.

2. All personnel who plan to PCS to the CENTCOM AOR will follow Service specific guidance as they would for any overseas PCS assignment. This includes an Exceptional Family Member Program (EFMP) assessment of all family members with appropriate approval from the receiving medical facility and/or TRICARE Eurasia.

a. Service Members or Service Members spouses who are either pregnant or become pregnant during their time in the CENTCOM AOR should not plan on delivering in the AOR and instead plan on delivering outside the AOR as directed by TRICARE Eurasia.

b. Due to a lack of both adult and child behavioral health resources, Service Members or family members with concerning behavioral health conditions will need to ensure approval as noted above before a PCS tour is approved.

3. While MOD 13 in its entirety does not apply to PCS personnel, the following sections will still apply as it pertains to Service Members and civilian employees. The word 'deployer' in MOD 13 and TAB A also applies to PCS personnel with regards to the following paragraphs;

a. 15.C.1.A-B. Medical Readiness Processing and Fitness for Duty
b. 15.C.2. Unfit Personnel
c. 15.D.1. Pharmacy Supply
d. 15.D.2.B-C. Psychotropic Medications and Controlled Substances
e. 15.D.4. TRICARE Mail Order Pharmacy (TMOP)
f. 15.E.2. Non-permitted Medical Equipment
g. 15.F. Immunizations
h. 15.H.1. Periodic Health Assessments (PHA)
i. 15.I.1.D. Medical Records
j. 15.L.8.A-B. Local Animal Contact
k. TAB A, 7.A-7.H. The noted medical conditions are not necessarily disqualifying for PCS if either the receiving medical facility (MTF) or TRICARE Eurasia agree to receive the Service Member and/or their family members.

EXHIBIT 56

MOD 13 TAB C **CENTCOM Medical Waiver Request**

Patient Name (Last, First): DOB: SSN(Last 4):

Previous Deployments: Destination (country): Diagnosis (Lay term):

Age: Sex: Grade: Service: Home Station:

Years of Service: Active/Reserve/Guard/Civilian: MOS/Job Description:

Deployment Length: Previous Waivers (Y/N): Currently Deployed (Y/N):

Waiver POC Name/E-mail/Phone:

Case Summary (To be completed by provider, including clinical information necessary to make a disposition. See most recent updated MOD 13 and accompanying PPG-TAB A for required information. Attach supporting medical documentation:

I have reviewed the case summary and hereby submit this request.

Signature:_____ Commander Approval:_____

CENTCOM Surgeon / Component Surgeon Response

Waiver Approval: ☐ **YES** ☐ **NO**

Signature:_____ Date:_____

DARIN K VIA
CAPT, MC, USN
CENTCOM Command Surgeon

Comments:

EXHIBIT 57

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Downloaded from https://aidsinfo.nih.gov/guidelines on 6/3/2020

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

What's New in the Guidelines? (Last updated December 18, 2019; last reviewed December 18, 2019)

Antiretroviral Therapy to Prevent Sexual Transmission of HIV (Treatment as Prevention)

Clinical trials have shown that using effective antiretroviral therapy (ART) to consistently suppress plasma HIV RNA levels to <200 copies/mL prevents transmission of HIV to sexual partners. When ART is used to prevent HIV transmission, this strategy is called treatment as prevention (TasP), commonly known as Undetectable = Untransmittable or U=U.

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) has added a new section to help providers integrate TasP into their clinical practice. The key recommendations include:

- Providers should inform persons with HIV that maintaining HIV RNA levels <200 copies/mL with ART prevents HIV transmission to sexual partners **(AII)**.
- Persons starting ART should use another form of prevention with sexual partners for at least the first 6 months of treatment and until an HIV RNA level of <200 copies/mL has been documented **(AII)**. Many experts recommend confirming sustained suppression before assuming that there is no risk of sexual HIV transmission **(AIII)**.
- Persons with HIV who rely on ART for prevention need to maintain high levels of ART adherence **(AIII)**. They should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII)**.
- Providers should inform patients that maintaining an HIV RNA level of <200 copies/mL does not prevent acquisition or transmission of other sexually transmitted infections **(AII)**.

Dolutegravir Recommendations for Individuals of Childbearing Potential

The latest data on neural tube defects (NTDs) in infants born to women who received dolutegravir (DTG) around the time of conception have shown that the prevalence of NTDs is lower than initially reported (the rate has been reduced from 0.9% to 0.3%). However, this rate is still higher than the rate reported for infants born to individuals who received ART that did not contain DTG (0.1%).

In the previous version of the guidelines, the Panel did not recommend the use of DTG in persons who are pregnant and within 12 weeks post-conception or persons of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception. Based on the new data, the Panel has revised these recommendations:

- Providers should discuss the benefits of using DTG and the risk of NTDs with the person of childbearing potential, to allow the person to make informed decisions about care.
- DTG may be used as an alternative antiretroviral (ARV) drug for individuals who are of childbearing potential and trying to conceive **(BII)** and those who are sexually active and not using contraception **(BII)**.
- For individuals who are using effective contraception, DTG may be used as a recommended option **(AII)**.
- Providers should refer to the Perinatal Guidelines for recommendations on the use of DTG during pregnancy.

More detailed recommendations on the use of DTG and other integrase strand transfer inhibitors (INSTIs) in persons of childbearing potential can be found in Table 6b, as well as in different sections of the guidelines where DTG is discussed.

Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy

The Panel previously recommended monitoring fasting lipid profile and fasting glucose before and after initiation of ART. The new recommendation allows for random (nonfasting) tests, in accordance with recommendations from the recently published blood cholesterol and diabetes management guidelines.

Initiation of Antiretroviral Therapy

The Panel emphasizes the importance of screening and early diagnosis of HIV. In order for persons with HIV to benefit from early diagnosis, the Panel recommends that ART be started immediately or as soon as possible after diagnosis to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression for individual patients, reduce the risk of HIV transmission, and improve the rate of virologic suppression among persons with HIV **(AII)**.

What to Start

Based on the results of two large, randomized controlled trials that showed that a two-drug regimen of DTG plus lamivudine (DTG/3TC) was noninferior to DTG plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), the Panel has added DTG/3TC to the list of *Recommended Initial Regimens for Most People with HIV*, **except for individuals**:

- With pre-treatment HIV RNA >500,000 copies/mL;
- Who are known to have active hepatitis B virus (HBV) coinfection; *or*
- Who will initiate ART before results of HIV genotype testing for reverse transcriptase or HBV testing are available.

Table 6b has been updated with revised recommendations on the use of DTG in individuals of childbearing potential.

Current data on the possible association between weight gain and the use of INSTIs and tenofovir alafenamide (TAF) are reviewed in the sections on INSTIs and nucleoside reverse transcriptase inhibitors.

Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression

This section has been updated with new clinical trial data from switch studies that were published or presented since the last revision.

The Panel emphasizes the importance of reviewing a patient's ART history and recognizing any past instances of treatment failure and drug resistance when selecting a new ART regimen. The Panel also emphasizes that using two-drug ART regimens is not recommended for persons with active HBV coinfection.

Acute and Recent (Early) HIV Infection

This section has been updated to emphasize the importance of initiating ART as soon as possible after diagnosis of acute and recent HIV infection **(AII)**.

Bictegravir/TAF/FTC has been added as a treatment option for persons with acute or recent HIV infection in cases where ART will be initiated before genotypic drug resistance testing results are available **(AIII)**.

HIV and the Older Person

This section has been updated with new data related to older persons with HIV. These updates focus on:

- The need to identify individuals who are at risk of HIV and the need for early diagnosis;

- The impact of age on HIV disease progression and the increase in age-related comorbidities; *and*
- The importance of initiating ART while being aware of the complexities of management in older persons with HIV due to polypharmacy and the potential for drug-drug interactions.

The Panel emphasizes the importance of recognizing and managing HIV-associated neurocognitive disorder (HAND), which may be associated with reduced ART adherence and poorer overall health outcomes. The Panel also recognizes that mental health disorders in older persons with HIV is a growing concern; screening for depression and management of depression are critical components of care for these patients.

Tuberculosis/HIV Coinfection

This section has been updated with newly published data on short-course regimens in the treatment of latent tuberculosis infection and new drug-drug interaction data for ARV drugs and rifampin and rifapentine.

Cost Considerations and Antiretroviral Therapy

Key updates to this section include:

- An overview of the individual and societal costs of HIV care in the United States.
- A new sub-section on cost sharing that describes how varying cost-containment practices may impact the out-of-pocket payments for patients with Medicaid, Medicare, and Ryan White (AIDS Drug Assistance Program) coverage. To help clinicians to better understand the different ART-related pricing systems in the United States, a new table entitled Table 19a. Insurance and Health Program Prescription Drug Pricing and Access was created.
- A revised discussion of ARV drug costs that highlights the increased cost of brand-name drugs and the impact that anticipated commercialization of additional generic-based regimens will have on the cost of ART.
- An updated discussion of the economic value of several HIV-specific laboratory tests.

Table Updates

The following tables have been updated using data that has become available since the last revision:

- Tables 17 and 18 in Adverse Effects of Antiretroviral Agents
- Drug-Drug Interactions Tables 21a-e, 22a, and 22b
- Appendix B: Drug Characteristics Tables

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List of Tables

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Members and Consultants (Last updated July 10, 2019; last reviewed July 10, 2019)

These guidelines were developed by the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (a working group of the Office of AIDS Research Advisory Council).

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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure for Companies Related to HIV Treatment or Diagnostics (Reporting Period: February 1, 2019, to January 31, 2020) (page 1 of 3)

Member	Status	Financial Disclosure	
		Company	Relationship
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		Gilead Sciences	Research Support
		GlaxoSmithKline	Advisory Board, Research Support
		Janssen Pharmaceutica	Advisory Board
		Medicure, Inc.	Consultant
		Merck & Co.	Advisory Board
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Danielle Campbell	M	ViiV Healthcare	Travel Support for attendance at a Community Summit
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Laura Cheever	M	None	N/A
Jennifer Cocohoba	M	Genentech	Supports the University of California San Francisco Pharmacy Fellowship program in Clinical Drug Development in Oncology; Dr. Cocohoba receives salary support for being the co-director of this program.
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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure for Companies Related to HIV Treatment or Diagnostics (Reporting Period: February 1, 2019, to January 31, 2020) (page 2 of 3)

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		Inovio Pharmaceuticals	Research Support
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		ViiV Healthcare	Research Support, Consultant

Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure for Companies Related to HIV Treatment or Diagnostics (Reporting Period: February 1, 2019, to January 31, 2020) (page 3 of 3)

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		CytoDyn	Research Support
		Frontier Biotechnologies, Inc	Research Support
		Gilead Sciences	Research Support
		GlaxoSmithKline	Research Support
		Merck, Sharpe, Dohme, Inc.	Research Support
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Key: C = Co-Chair; ES = Executive Secretary; M = Member; PI = Principal Investigator

Introduction (Last updated December 18, 2019; last reviewed December 18, 2019)

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition, with life expectancy approaching that for people without HIV.[1,2] ART is also highly effective at preventing sexual transmission of HIV in patients who have adequately suppressed viral loads.[3-5] Unfortunately, in 2016, only 51% of people with HIV in the United States had maximally suppressed viral loads;[6] the lack of suppression is mostly due to undiagnosed HIV infection and failure to link or retain patients with HIV in care.

The Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The Panel's primary goal is to provide HIV care practitioners with recommendations that are based on current knowledge of the antiretroviral (ARV) drugs that are used to treat adults and adolescents with HIV in the United States. The Panel reviews new evidence and updates recommendations when needed. These guidelines include recommendations on baseline laboratory evaluations, treatment goals, benefits of ART and considerations when initiating therapy, choice of the initial regimen for ART-naive persons with HIV, ARV drugs or combinations to avoid, management of treatment failure, optimizing ART regimens, management of adverse effects and drug interactions, and special ART-related considerations in specific populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV to provide recommendations for adolescents at different stages of growth and development. Recommendations for ART regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., those with sexual maturity ratings [SMRs] of 4 and 5). Clinicians should follow recommendations in the Pediatric Antiretroviral Guidelines when initiating ART in adolescents with an SMR of 3 or lower. For recommendations related to pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention.[7]

These guidelines represent current knowledge regarding the use of ARV drugs. Because the science of HIV evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not always be consistent with approved labeling for the specific drugs or indications, and the use of the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration-defined legal standards for drug approval. The Panel frequently updates the guidelines (current and archived versions of the guidelines are available on the AIDS*info* website). However, updates to the guidelines may not keep pace with the release of new data, and the guidelines cannot offer guidance on care for all patients. Patient management decisions should be based on clinical judgement and attention to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART and encourages both the development of protocols and patient participation in well-designed, Institutional Review Board-approved clinical trials.

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in patients with HIV are better when care is delivered by clinicians with HIV expertise (e.g., those who have cared for a large panel of patients with HIV),[8-12] reflecting the complexity of HIV transmission and its treatment. Appropriate training, continuing education, and clinical experience are all components of optimal care. Providers who do not have this requisite training and experience should consult HIV experts when needed.

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents for the treatment of HIV in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 50 voting members who have expertise in HIV care and research and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are nongovernmental scientific members. The Panel also includes four to five community members with knowledge of HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open call for nominations. Each member serves on the Panel for a 4-year term with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members.
Financial disclosure	All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infection. The latest version of the Financial Disclosure list is available on the AIDS*info* website.
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer reviewed journals or data available in FDA drug labels. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the section's area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines.
Other guidelines	These guidelines focus on antiretroviral therapy (ART) for adults and adolescents with HIV. For a more detailed discussion on the use of ART in children and prepubertal adolescents (those with sexual maturity ratings of 1 to 3), clinicians should refer to the Pediatric Antiretroviral Guidelines. These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women. For more details on the use of ARV drugs during pregnancy, see the Perinatal Guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information relating to ARV drugs that may have an impact on the clinical care of persons with HIV. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the AIDS*info* website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDS*info* website.
Public comments	A 2-week public comment period follows the release of the updated guidelines on the AIDS*info* website. The Panel reviews comments to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation statement includes a letter (**A**, **B**, or **C**) that represents the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that represents the quality of the evidence that supports the recommendation (see Table 2).

Table 2. Rating Scheme for Recommendations

Strength of Recommendation[i]	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

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Baseline Evaluation (Last updated May 1, 2014; last reviewed May 1, 2014)

Every patient with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and to initiate care as recommended in HIV primary care guidelines[1] and guidelines for prevention and treatment of HIV-associated opportunistic infections.[2] The initial evaluation also should include discussion on the benefits of antiretroviral therapy (ART) for the patient's health and to prevent HIV transmission. Baseline information then can be used to define management goals and plans. In the case of previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete antiretroviral (ARV) history (including drug resistance testing results, if available), preferably through the review of past medical records. Newly diagnosed patients should also be asked about any prior use of ARV agents for prevention of HIV infection.

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of ARV drug regimens:

- HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**;
- CD4 T lymphocyte cell count (CD4 count) **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN), and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**;
- Fasting blood glucose and serum lipids **(AIII)**; and
- Genotypic resistance testing **(AII)**. For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful **(BII)**.

In addition, other tests (including screening tests for sexually transmitted infections and tests for determining the risk of opportunistic infections and need for prophylaxis) should be performed as recommended in HIV primary care and opportunistic infections guidelines.[1,2]

Patients living with HIV infection often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centered, multi-disciplinary approach to the disease. The baseline evaluation should include an evaluation of the patient's readiness for ART, including an assessment of high-risk behaviors, substance abuse, social support, mental illness, comorbidities, economic factors (e.g., unstable housing), medical insurance status and adequacy of coverage, and other factors that are known to impair adherence to ART and increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly. The baseline evaluation should also include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission.

Education about HIV risk behaviors and effective strategies to prevent HIV transmission should be provided at each patient visit.

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Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy (Last updated December 18, 2019; last reviewed December 18, 2019)

Several laboratory tests are important for initial evaluation of people with HIV upon entry into care, and some tests should be performed before and after initiation or modification of antiretroviral therapy (ART) to assess the virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. Table 3 outlines recommendations on the frequency of testing from the Panel on Antiretroviral Guidelines for Adults and Adolescents. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used to monitor people with HIV: plasma HIV RNA (viral load) to assess level of HIV viremia and CD4 T lymphocyte cell count to assess immune function. Standard (reverse transcriptase and protease) genotypic resistance testing should be used to guide selection of an ARV regimen; if transmitted integrase strand transfer inhibitor resistance is a concern, testing should also include the integrase gene (see Drug-Resistance Testing). For guidance on ART regimens to use when resistance testing results are unavailable, clinicians should consult What to Start. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist. HLA-B*5701 testing should be performed before initiation of abacavir (ABC). Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART and, if indicated, periodically after ART initiation, as treatment of these coinfections may affect the choice of ART and likelihood of drug-induced hepatotoxicity. The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the guidelines.

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 4)

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Cell Count	√	√		√ During first 2 years of ART, or if viremia develops while patient is on ART, or if CD4 count is <300 cells/mm^3		√ **After 2 Years on ART with Consistently Suppressed Viral Load** *CD4 Count 300–500 cells/mm^3:* • Every 12 months *CD4 Count >500 cells/mm^3:* • CD4 monitoring is optional.	√	√	√ Every 3–6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional.
Resistance Testing	√[f]	√[f]					√[f]	√[f]	√[f]
HLA-B*5701 Testing		√ If considering ABC							
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist, or for patients experiencing virologic failure on a CCR5 antagonist-based regimen	√	

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a] (page 2 of 4)

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)[g,h,i]	√	√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]				√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]		√ Including prior to starting HCV DAA (see HCV/HIV Coinfection)	
Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)[j]	√					√ Repeat HCV screening for at-risk patients[k]		√	
Basic Chemistry[l,m]	√	√	√		√			√	√ Every 6–12 months
ALT, AST, Total Bilirubin	√	√	√		√			√	√ Every 6–12 months
CBC with Differential[n]	√	√		√ When monitoring CD4 cell count; perform CBC cell count and CD4 concurrently		√ When no longer monitoring CD4 cell count		√	√ Every 3–6 months
Random or Fasting Lipid Profile[o]	√	√				√		√	√ If normal at baseline, annually
Random or Fasting Glucose[p]	√	√				√		√	√ If normal at baseline, annually

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a] (page 3 of 4)

Laboratory Test	Timepoint or Frequency of Testing								
	Entry Into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Urinalysis[m,q]	√	√			√ If on TDF[l]	√		√	
Pregnancy Test[r]	√	√						√	

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care Guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] If ART is initiated soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] ART is indicated for all individuals with HIV and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

[d] If HIV RNA is detectable at 2–8 weeks, repeat testing every 4–8 weeks until viral load is suppressed to <200 copies/mL. Thereafter, repeat testing every 3–6 months.

[e] In patients on ART, viral load typically is measured every 3–4 months. More frequent monitoring may be considered in individuals who are having difficulties with ART adherence. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

[f] Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase and protease genes. If transmitted INSTI resistance is a concern or if a person presents with viremia while on an INSTI, providers should also test for resistance mutations to this class of drugs. In ART-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if resistance testing was performed at entry into care. In patients with virologic suppression who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; see the section on Drug Resistance Testing for discussion of the potential limitations and benefits of proviral DNA assays in this situation. Results from prior resistance testing can be helpful in constructing a new regimen.

[g] If patient has HBV infection (as determined by a positive HBsAg or HBV DNA test result), TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections (HBV/HIV).

[h] If HBsAg, HBsAb, and HBcAb test results are negative, hepatitis B vaccine series should be administered. Refer to the HIV Primary Care Guidelines and the Adult and Adolescent Opportunistic Infection Guidelines for detailed recommendations.[1,2]

[i] Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load test for confirmation. If the HBV viral load test is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If the test is negative, the patient should be vaccinated. Refer to the HIV Primary Care Guidelines and the Adult and Adolescent Opportunistic Infection Guidelines for more detailed recommendations.[1,2]

[j] The HCV antibody test may not be adequate for screening in the setting of recent HCV infection (defined as acquisition within the past 6 months), or advanced immunodeficiency (CD4 count <100 cells/mm^3). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

[k] Injection drug users, persons with a history of incarceration, men with HIV who have unprotected sex with men, and persons with percutaneous/parenteral exposure to blood in unregulated settings are at risk of HCV infection.

Table 3. Laboratory Testing Schedule for Monitoring People with HIV Before and After Initiation of Antiretroviral Therapy[a] (page 4 of 4)

[l] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose, and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TDF-containing regimens.[3]

[m] Consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America for recommendations on managing patients with renal disease.[3] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

[n] CBC with differential should be done when a CD4 count is performed. When CD4 count is no longer being monitored, the recommended frequency of CBC with differential is once a year. More frequent monitoring may be indicated for persons who are receiving medications that potentially cause cytopenia (e.g., ZDV, TMP-SMX).

[o] If random lipids are abnormal, fasting lipids should be obtained. Consult the 2018 Guideline on the Management of Blood Cholesterol for diagnosis and management of patients with dyslipidemia.[4]

[p] If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in persons with HIV on ART (see the ADA Guidelines).[5]

[q] Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

[r] For people of childbearing potential.

Key: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CD4 = CD4 T lymphocyte; Cl = chloride; DAA = direct-acting antiviral; FTC = emtricitabine; HbA1C = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring (Last updated May 1, 2014; last reviewed May 1, 2014)

HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell count are the two surrogate markers of antiretroviral treatment (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.[1] The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy **after** initiation of ART.

Measurement of CD4 count is particularly useful **before** initiation of ART. The CD4 cell count provides information on the overall immune function of a person with HIV. The measurement is critical in establishing thresholds for the initiation and discontinuation of opportunistic infection (OI) prophylaxis and in assessing the urgency to initiate ART.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. In the United States, ART is now recommended for all patients with HIV regardless of their viral load or CD4 count **(AI)** (see Initiation of Antiretroviral Therapy). In the past, clinical practice, which was supported by treatment guidelines, was generally to monitor both CD4 cell count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

Plasma HIV-1 RNA (Viral Load) Monitoring

Viral load is the most important indicator of initial and sustained response to ART **(AI)** and should be measured in all patients with HIV at entry into care **(AIII)**, at initiation of therapy **(AIII)**, and on a regular basis thereafter. For those patients who choose to delay therapy, repeat viral load testing while not on ART is optional **(CIII)**. Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see What to Start). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see HIV-2 Infection.

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-3] Thus, viral load testing is an established surrogate marker for treatment response.[4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 $\log_{10}$ copies/mL change). Optimal viral suppression is defined generally as a viral load persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not predictive of virologic failure.[5] Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One recent study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.[6-9] These guidelines and the AIDS Clinical Trials Group (ACTG) now define virologic failure as a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see Virologic Failure and Suboptimal Immunologic Response).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it

may take longer. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART or modification of therapy because of virologic failure.** Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification **(AIII)**. The purpose of the measurements is to confirm an adequate initial virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII)**.
- **In virologically suppressed patients in whom ART was modified because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy **(AIII)**. The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load should be repeated every 3 to 4 months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable **(AIII)**.
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen (see Drug-Resistance Testing and Virologic Failure and Suboptimal Immunologic Repsonse sections).

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies.[11,12] CD4 counts are highly variable; a significant change (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it is **not routinely recommended (BIII)**.

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all patients at entry into care **(AI)**. It is the key factor in determining the need to initiate OI prophylaxis (see the Adult Opportunistic Infection Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiating Antiretroviral Therapy section of these guidelines). Although most OIs occur in patients with CD4 counts <200 cells/mm^3, some OIs can occur in patients with higher CD4 counts.[14]

Use of CD4 Count for Monitoring Therapeutic Response

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult Opportunistic Infection Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm^3 during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 to 100 cells/mm^3 per year until a steady state level is reached.[15] Patients who initiate therapy with a low CD4 count[16,17] or at an older age[18] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is now recommended for all patients with HIV. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis **(AIII)**.

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII)**. This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the guidelines for treatment and prophylaxis of opportunistic infections.[13] In this setting, and in the first 2 years following ART initiation, CD4 count can be monitored at 3- to 6- month intervals **(BII)**.

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 count provides limited information. Frequent testing is unnecessary because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm^3 are rare in patients with viral suppression and CD4 counts >300 cells/mm^3.[19] Similarly, the ARTEMIS trial found that CD4 monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[20] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 and 200 cells/mm^3.[21] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes such as cardiovascular disease, malignancy, and death.[22] An analysis of costs associated with CD4 monitoring in the United States estimated that reducing CD4 monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.[23]

For the patient on a suppressive regimen whose CD4 count has consistently ranged between 300 and 500 cells/mm^3 for at least 2 years, the Panel recommends CD4 monitoring on an annual basis **(BII)**. Continued CD4 monitoring for virologically suppressed patients whose CD4 counts have been consistently >500 cells/mm^3 for at least 2 years may be considered optional **(CIII)**. The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient's clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 cell count (e.g., interferon, chronic corticosteroids, or antineoplastic agents) **(AIII)**. In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months **(AIII)** (see Virologic Failure and Suboptimal Immunologic Response).

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy[24,25] or coinfection with human T-lymphotropic virus type I (HTLV-1)[26] may cause misleadingly elevated CD4 counts. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage.[27] In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care **(AIII)** If ART initiation is deferred, repeat before initiating ART **(AIII)**. In patients not initiating ART, repeat testing is optional **(CIII)**.	At entry into care **(AI)** If ART is deferred, every 3 to 6 months[b] **(AIII)**
After initiating ART	Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART **(AIII)**; thereafter, every 4 to 8 weeks until viral load is suppressed **(BIII)**.	3 months after initiation of ART **(AIII)**
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen **(AIII)**.	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification **(AIII)**; thereafter, every 4 to 8 weeks until viral load is suppressed **(BIII)**. If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated **(AIII)**.	Every 3 to 6 months **(AI)**
During the first 2 years of ART	Every 3 to 4 months **(AIII)**	Every 3 to 6 months[a] **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII)**.	Every 12 months **(BII)**
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)		Optional **(CIII)**
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months **(AIII)** or more frequently if clinically indicated (see Virologic Failure).	Every 3 to 6 months **(AIII)**
Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months **(AIII)**	Perform CD4 count and repeat as clinically indicated[c] **(AIII)**

[a] Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

[b] Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm^3).

[c] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

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Drug-Resistance Testing (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

For Antiretroviral Therapy-Naive Persons:

- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen **(AII)**. If therapy is deferred, repeat testing may be considered at the time of ART initiation **(CIII)**.
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**.
- In persons with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported **(AIII)**.
- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes the integrase gene **(AIII)**.

For Antiretroviral Therapy-Experienced Persons:

- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ART regimens in the following patients:
  - Persons with virologic failure and HIV RNA levels >1,000 copies/mL **(AI)**
  - Persons with HIV RNA levels >500 copies/mL but <1,000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered **(BII)**
  - Persons with suboptimal viral load reduction **(AII)**
- When a person with HIV experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance (which may need to be ordered separately) should be performed to determine whether to include a drug from this class in subsequent regimens **(AII)**.
- Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if that is not possible, within 4 weeks after discontinuing therapy **(AII)**. If more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed due to lack of drug-selective pressure **(CIII)**.
- Genotypic testing is preferred over phenotypic resistance testing to guide therapy in persons with suboptimal virologic response or virologic failure while on first- or second-line regimens and in individuals in whom resistance mutation patterns are known or not expected to be complex **(AII)**.
- The addition of phenotypic to genotypic resistance testing is recommended for persons with known or suspected complex drug-resistance mutation patterns (BIII).
- All prior and current drug-resistance test results, if available, should be considered when constructing a new regimen for a patient **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and select treatment strategies. These assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). In some circumstances, INSTI-resistance tests may need to be ordered separately, and clinicians should check this with the testing laboratory. INSTI-resistance testing is particularly important in persons who experience virologic failure while taking an INSTI-containing regimen. Testing for fusion inhibitor resistance can also be ordered separately. There is currently no commercially available resistance test for the CD4 T lymphocyte post-attachment inhibitor ibalizumab. For a description of co-receptor tropism testing, see Co-receptor Tropism Assays.

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes; in general, these assays require a plasma viral load of at least 500 to 1,000 copies/mL. Most genotypic assays involve conventional Sanger sequencing of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes of circulating RNA in plasma to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene associated with resistance to the fusion inhibitor enfuvirtide is also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpreting these test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains an updated list of significant resistance-associated mutations in the RT, PR, IN, and envelope genes. The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results.[1] Various additional tools are also available to assist providers in interpreting genotypic test results.[2-5] Clinical trials have demonstrated that consulting with specialists in HIV drug resistance improves virologic outcomes.[6] Clinicians are thus encouraged to consult a specialist to interpret genotypic test results and design optimal new regimens.

A next-generation sequencing genotypic resistance assay that analyzes HIV-1 proviral DNA in host cells is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection or with low-level viremia.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT, PR, and, more recently, IN and envelope gene sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [IC_{50}]) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpreting phenotypic assay results can be complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) associated with drug failure, although clinically significant fold increase cutoffs have been described for some drugs.[7-11] Again, consulting with a specialist to interpret test results can be helpful.

Limitations of Genotypic and Phenotypic Assays

Limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important to note because a wild-type virus often re-emerges as the predominant population in the plasma after discontinuation of drugs that exert selective pressure on drug-resistant populations. As a consequence, the proportion of virus with resistance mutations can decrease to below the 10% to 20% threshold.[12-14] In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus.[15] Therefore, resistance testing is most valuable when performed while a person experiencing virologic failure is still taking ARV drugs or, if that is not possible,

then within 4 weeks after discontinuing therapy **(AII)**. Because resistant viruses may persist longer in the plasma of some patients, resistance testing that is done 4 to 6 weeks after discontinuation of drugs or later may still detect mutations and provide useful information to guide therapy **(CIII)**. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens. Importantly, in addition to considering prior antiretroviral therapy (ART) history, prior genotypic- or phenotypic-resistance test results should be obtained from old records when possible. Because the most current drug-resistance test may not be able to detect resistance mutations that were previously detected, these prior test results are clinically important and should be used when designing a new regimen **(AIII)**.

A next-generation sequencing genotypic assay that analyzes HIV-1 proviral DNA may provide additional information on drug resistance in patients with low levels of plasma HIV RNA or in patients whose levels are below the limit of detection **(CIII)**. However, these assays might miss some or all the previous drug-resistance mutations, and they should be interpreted with caution. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Clinical Practice (See Table 5)

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART.[16-19] The risk of acquiring drug-resistant virus is related to the prevalence of drug resistance in people with HIV who engage in high-risk behaviors within a given community. In high-income countries, approximately 10% to 17% of ART-naive individuals have resistance mutations to at least one ARV drug.[20] Up to 8%, but generally <5%, of transmitted viruses will exhibit resistance to drugs from more than one class.[20-23] Transmitted resistant HIV is generally either NNRTI- or NRTI-resistant. Transmitted PI resistance is much less common, and to date, transmitted INSTI resistance is rare.[24,25]

Resistance testing can guide therapy selection to optimize virologic response in people with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis. Therefore, resistance testing in these situations is recommended (AII). A genotypic assay is preferred for this purpose **(AIII)**. In these settings, treatment initiation should not be delayed pending resistance testing results if the individual is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see also Acute and Recent HIV [Early] Infection). In the absence of ART, resistant viruses may decline over time to less than the detection limit of standard resistance tests. However, when ART is eventually initiated, even low levels of resistant viruses may still increase the risk of treatment failure.[26-28] Therefore, if ART is deferred, resistance testing should still be performed during early HIV infection **(AIII)**. In this situation, the genotypic resistance test result should be used for regimen selection when the person begins ART. Repeat resistance testing at the start of treatment may also be considered, because a patient may acquire drug-resistant virus (i.e., superinfection) between entry-into-care and the initiation of ART (CIII).[29]

Interpretation of drug-resistance testing before ART initiation in persons with chronic HIV is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.[30-32] Though no prospective trial has directly addressed whether drug-resistance testing before initiation of therapy confers benefit in this population, data from several studies, including one prospective clinical trial, suggest that virologic responses in persons with baseline resistance mutations are suboptimal.[16-19,33-37] In addition, an analysis of early RT and PR genotypic resistance testing in ARV-naive persons suggests that baseline testing in this population is cost effective and should be performed.[38] Therefore, resistance testing in people with chronic infections is recommended at the time of entry into HIV care **(AII)**.

Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred over phenotypic testing because of lower cost, more rapid turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier interpretation of test results **(AIII)**. If therapy is deferred, repeat testing shortly before initiating ART may be considered, because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.[29] Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the RT and PR genes. Although reports of transmission of INSTI-resistant virus are rare, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers should supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs, which may need to be ordered separately **(AIII)**.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA in host cells can be considered when conventional HIV RNA drug resistance testing is unsuccessful or unavailable for patients initiating therapy **(CIII)**. As outlined above, the results should be interpreted with caution, as this assay might miss some or all previously existing drug-resistance mutations.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are important tools to inform treatment decisions for patients who experience virologic failure while on ART. Several prospective studies have assessed the utility of resistance testing to guide ARV drug selection in patients who experience virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6,39-45] In general, these studies found that changes in therapy based on resistance test results produced better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that the use of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[46] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see also Virologic Failure). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Conventional drug-resistance testing in persons with plasma viral loads <500 copies/mL is not usually recommended, because resistance assays cannot be consistently performed at low HIV RNA levels **(AIII)**.

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of ART is, for certain patients, associated with resistance to only one component of the regimen.[47-49] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotyping is preferred for resistance testing in patients who experience virologic failure or suboptimal viral load reduction while on a first or second ARV drug regimen and in individuals in whom resistance mutation patterns are known or not expected to be complex (i.e., mutations that are straightforward, usually limited in number, and/or those that have clear significance) (AII). Often in these situations, the mutation patterns detected can be interpreted by algorithms used to predict the impact of subsequent regimens on virologic response. For patients with extensive treatment history, complex mutational patterns may occur. In such situations, the interpretation of complex genotypes and the impact of the mutation pattern on subsequent treatment regimens can be challenging. For these individuals, phenotypic resistance testing may provide additional helpful information **(BIII)**. Rather than only predicting the impact of the detected mutations, these assays can measure *in vitro* the actual fold change in drug susceptibility, as well as the actual impact of mutation combinations and interactions on each drug under consideration.

When compared with phenotypic testing, genotypic testing costs less to perform and has a faster turnaround time

and greater sensitivity for detecting mixtures of wild-type and resistant virus. In addition, observations show that genotypic and phenotypic assays are comparable predictors of virologic response to subsequent ART regimens.[50] In patients who experience virologic failure while on INSTI-based regimens, testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**. In this circumstance, clinicians should confirm that, when they order a resistance test, their laboratory is testing for INSTI resistance in addition to NNRTI, NRTI, and PI resistance. If INSTI-resistance testing needs to be ordered separately (as is the case in some laboratories), clinicians should request this assay in addition to standard drug-resistance testing. Addition of phenotypic to genotypic testing is generally indicated for persons with known or suspected complex drug-resistance mutation patterns **(BIII)**.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for patients who are experiencing treatment failure and for whom conventional HIV RNA genotypic drug-resistance testing is unavailable or unsuccessful **(CIII)**. As outlined above, results should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).

Use of Resistance Assays for Optimizing Antiretroviral Regimen in Persons with Viral Suppression

In the past decade, simpler, more potent, and better-tolerated ARV medications have become available and new ARV drugs will likely continue to emerge. Switching individual ARV drugs in a regimen is sometimes considered for patients with a suppressed viral load in order to simplify a regimen, avoid drug interactions or toxicity, or for other reasons. Because the patient's viral load is suppressed, standard drug-resistance testing will not be successful.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for these individuals, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals who have experienced no prior virologic failures and who are on their first or second regimen, or who have genotypic testing results from when they had prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide additional useful information. However, in individuals who have experienced multiple prior failures, a prolonged history of prior ARV regimens, and/or for whom prior genotypic resistance test results are not available, it may be appropriate to utilize proviral DNA genotypic testing **(CIII)**. When such testing is obtained, results should be combined with all prior genotypic and phenotypic test results to construct a cumulative genotype, which incorporates all current and previously detected drug-resistance mutations. Results from this test should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Pregnancy

In pregnancy, the goal of ART is to rapidly and maximally reduce plasma HIV RNA to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant persons with HIV before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing in those found to have complex drug-resistance mutation patterns may provide additional information **(BIII)**. Optimal prevention of perinatal transmission requires prompt initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting and Recommendation	Rationale
In Acute or Recent (Early) HIV Infection: Drug-resistance testing is recommended **(AII)**. A genotypic assay is generally preferred **(AIII)**. Treatment should not be delayed while awaiting results of resistance testing **(AIII)**.	Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified, if necessary, once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing may be considered when therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-Naive Patients with Chronic HIV: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART **(AII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV.
For pregnant persons, or if ART will be initiated on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.	If necessary, the ART regimen can be modified once resistance test results are available.
If an INSTI is considered for an ART-naive patient **and/or** transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately **(AIII)**.	Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings.
If therapy is deferred, repeat resistance testing may be considered before initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing before initiation of ART may be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)**.	See Co-Receptor Tropism Assays section.
In Patients with Virologic Failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**.	Drug-resistance testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen.
Resistance testing should be done while the patient is taking ART or, if that is not possible, within 4 weeks after ART discontinuation **(AII)**. If >4 weeks have elapsed, resistance testing may still be useful to guide therapy; however, previously-selected mutations can be missed due to lack of drug selective pressure **(CIII)**.	The absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens, as mutations may decay with time.
A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens and for those with noncomplex resistance patterns **(AII)**.	Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV.
All prior and current drug-resistance testing results should be reviewed and considered when designing a new regimen for a patient experiencing virologic failure **(AIII)**.	Drug resistance mutations may decay with time, and mutations detected in prior resistance tests may not be detected in current tests, though they remain clinically relevant.
When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**.	Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory).

Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting and Recommendation	Rationale
Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns **(BIII)**.	Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns.
In Patients with Suboptimal Suppression of Viral Load: Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART **(AII)**.	Testing can determine the role of resistance in suboptimal viral suppression, and it can help the clinician identify the number of active drugs available in the current regimen and assess the need for a new regimen.
In Pregnant Persons with HIV: Genotypic resistance testing is recommended for all pregnant persons before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goals of ART in pregnant persons with HIV are to achieve maximal viral suppression for treatment of maternal HIV and to prevent perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available, if needed.
In Patients with Undetectable Viral Load or Low-Level Viremia: HIV-1 proviral DNA resistance assays may be useful in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV RNA genotypic assay is unlikely to be successful **(CIII)**.	This test may provide information about previously circulating resistant viral variants that are archived within proviral DNA. These assays may miss some or all prior resistance mutations that have occurred within the viral quasi-species, and therefore they should be interpreted with caution. The clinical utility of HIV-1 proviral DNA assays has not been fully determined.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

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Co-Receptor Tropism Assays (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations
• A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**. • Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**. • A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI)**. • A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII)**. • A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) **(BII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV enters cells by a complex process that involves sequential attachment to the CD4 T lymphocyte (CD4) receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes.[1] CCR5 co-receptor antagonists prevent HIV entry into target cells by binding to the CCR5 receptors.[2] Phenotypic and genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., use of CCR5, CXCR4, or both as either dual-tropic virus or a mixed population of viruses referred to for purposes of assay results as dual/mixed [D/M]) of the patient's dominant virus population. An older generation assay (Trofile,® Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in clinical trials that led to the approval of maraviroc (MVC), the only CCR5 antagonist currently available. The assay has been improved and is now available with enhanced sensitivity. In addition, genotypic assays to predict co-receptor usage are commercially available.

During acute/recent infection, the vast majority of patients harbor a CCR5-utilizing virus (R5 virus), which suggests that the R5 variant is preferentially transmitted; however, up to 19% of individuals with acute/recent infection can harbor CXCR4-tropic virus.[3-5] Viruses in many untreated patients eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 usage or D/M tropism. This shift is temporally associated with a more rapid decline in CD4 counts,[6,7] but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.[1] Antiretroviral-treated patients with extensive drug resistance or persistently high-level viremia are more likely to harbor CXCR4- or D/M-tropic variants than untreated patients with comparable CD4 counts.[8,9] The prevalence of CXCR4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.[8,10] Since CXCR4-tropic viruses may be present at initial presentation or a patient may shift to CXCR4-tropism over the course of infection, co-receptor tropism should always be assessed prior to the use of CCR5 antagonists for treatment. Once a patient has ever been documented with detectable CXCR4- or D/M-tropic virus, it is assumed that such viruses will always be present. CCR5 co-receptor antagonists will no longer be active for that patient and should not be used.

Phenotypic Assays

Phenotypic assays characterize the co-receptor usage of plasma-derived virus. These assays involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses, which are replication-defective, are used to infect target cell lines that express either CCR5 or CXCR4.[11,12] Using the Trofile® assay, the co-receptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. This assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the Trofile® assay.[12] This earlier assay failed to routinely detect low levels of CXCR4 utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low levels of such variants at baseline, which were below the assay limit of detection, and these patients exhibited rapid virologic failure after initiation of a CCR5 antagonist.[13] The assay has been improved and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones represent 0.3% or more of the virus population.[14] Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only assay that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the Trofile® assay.

In patients with an undetectable viral load or detectable plasma HIV RNA <1,000 copies/mL, phenotypic co-receptor usage can be determined using proviral DNA obtained from peripheral blood mononuclear cells (e.g., Trofile® DNA, Monogram Sciences); however, the clinical utility of this assay remains to be determined.[15]

Genotypic Assays

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 *env*, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence.[16] When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50% to 75%) for the presence of a CXCR4-utilizing virus. Studies in which V3 genotyping was performed on samples from patients screened for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC.[17-19] An important caveat is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (Trofile®). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. Other studies have also demonstrated relatively high concordance between genotypic- and phenotypic-assessed tropism;[20,21] however, there is variability between different genotypic platforms.[22]

Given these performance characteristics, genotypic tropism assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant;[23] therefore, the Panel preferentially recommends phenotypic testing. Based on accessibility, capacity, logistics, and cost, European guidelines currently include genotypic testing as an equivalent option to phenotypic testing when determining co-receptor usage among patients with HIV RNA >1,000 copies/mL and preferentially for those with HIV RNA ≤1,000 copies/mL.[24]

HIV-1 proviral DNA genotypic tropism testing is available for patients with HIV RNA <1,000 copies/mL. These assays evaluate the HIV-1 proviral DNA integrated within infected cells for CXCR4-utilizing viral strains.[25] As discussed above, caution is advised when using such assays, as their detection limit, concordance with plasma HIV RNA tropism, and clinical utility are not yet fully determined.

Use of Assays to Determine Co-receptor Usage in Clinical Practice

An assay for HIV-1 co-receptor usage should be performed whenever the use of a CCR5 antagonist is being considered **(AI)**. This is true even in the setting of prior tropism testing showing CCR5 usage, as viral evolution may occur over the course of infection. In addition, because virologic failure may occur due to a shift from CCR5-using to CXCR4-using virus, testing for co-receptor usage is recommended in patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**. Virologic failure may also be caused by resistance of a CCR5-using virus to a CCR5 antagonist, but such resistance is uncommon. Compared to genotypic testing, phenotypic testing has more evidence supporting its utility. Therefore, a phenotypic test for co-receptor usage is generally preferred **(AI)**. However, because phenotypic testing is more expensive, requires more time to

perform, and may have logistic challenges, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII)**.

As with HIV resistance testing, the results of all prior tropism tests should be obtained. If CXCR4-utlizing or D/M-tropic viruses have ever been detected previously, then repeat testing is not necessary and a CCR5 co-receptor antagonist **should not be used**.

If a CCR5 co-receptor antagonist is being considered in a patient with an undetectable HIV RNA (e.g., in cases of regimen simplification or a toxicity-related switch), a proviral DNA tropism assay can be utilized **(BII)**.[26-28] If CXCR4-utlizing or D/M-tropic viruses are detected, then the CCR5 co-receptor antagonist **should not be used**.

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HLA-B*5701 Screening (Last updated December 1, 2007; last reviewed January 10, 2011)

Panel's Recommendations
• The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) **(AI)**. • HLA-B*5701-positive patients should not be prescribed ABC **(AI)**. • The positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. • When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR **(CIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The abacavir (ABC) hypersensitivity reaction (HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5% to 8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.[1]

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701.[2,3] Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR.[4] A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele.[5] The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized participants with HIV before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC).[6] The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations).[7]

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting an ABC-containing regimen in a person with HIV **(AI)**. HLA-B*5701–positive patients should not be prescribed ABC **(AI)**, and the positive status should be recorded as an ABC allergy in the patient's medical record (AII). HLA-B*5701 testing is needed only once in a patient's lifetime; thus, efforts to carefully record and maintain the test result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701–positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening

is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

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Treatment Goals (Last updated January 28, 2016; last reviewed January 28, 2016)

Antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality at all stages of HIV infection[1-4] and has reduced HIV transmission.[5-8] Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 T lymphocyte (CD4) cell numbers, and confers substantial clinical benefits, all of which are important treatment goals.[9,10] HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in cohorts with HIV (see Initiating Antiretroviral Therapy). Despite these benefits, eradication of HIV infection cannot be achieved with available antiretrovirals (ARVs). Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality.[11] Thus, once initiated, ART should be continued, with the following key treatment goals:

- Maximally and durably suppress plasma HIV RNA;
- Restore and preserve immunologic function;
- Reduce HIV-associated morbidity and prolong the duration and quality of survival; and
- Prevent HIV transmission.

Achieving viral suppression currently requires the use of combination ARV regimens that generally include three active drugs from two or more drug classes. Baseline patient characteristics and results from drug resistance testing should guide design of the specific regimen (see What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient). When initial HIV suppression is not achieved or not maintained, changing to a new regimen with at least two active drugs is often required (see Virologic Failure).The increasing number of ARV drugs and drug classes makes viral suppression below detection limits an achievable goal in most patients.

After initiation of effective ART, viral load reduction to below limits of assay detection usually occurs within the first 12 to 24 weeks of therapy. Predictors of virologic success include the following:

- Low baseline viremia;
- High potency of the ARV regimen;
- Tolerability of the regimen;
- Convenience of the regimen; and
- Excellent adherence to the regimen.

Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

Several ARV regimens are recommended for use in ART-naive patients (see What to Start). Most of the recommended regimens have comparable efficacy but vary in pill burden, potential for drug interactions and/or side effects, and propensity to select for resistance mutations if ART adherence is suboptimal. Regimens should be tailored for the individual patient to enhance adherence and support long-term treatment success. Considerations when selecting an ARV regimen for an individual patient include potential side effects, patient comorbidities, possible interactions with conconcomitant medications, results of pretreatment genotypic drug-resistance testing, and regimen convenience (see Table 7).

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient-related factors, such as active substance abuse, depression, or

the experience of adverse effects; and health system issues, including interruptions in patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART (see Adherence to the Continuum of Care).

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Initiation of Antiretroviral Therapy (Last updated December 18, 2019; last reviewed December 18, 2019)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)**.
- The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV **(AII)**.
- When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

The primary goal of antiretroviral therapy (ART) is to prevent HIV-associated morbidity and mortality. This goal is accomplished by using effective ART to achieve and maintain a plasma HIV-1 RNA (viral load) below the quantification limits of commercially available assays. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS–defining complications, and allows persons with HIV to live a lifespan approaching that of persons without HIV.[1]

Another goal of ART is to reduce the risk of HIV transmission to sexual partners and to infants born to persons with HIV. High plasma HIV RNA levels are a major risk factor for HIV transmission; effective ART can reduce both viremia and the risk of transmission of HIV to sexual partners[2-6] and prevent perinatal transmission.[7,8] Modelling studies and ecological studies of populations with high ART uptake and high viral suppression rates suggest that expanded use of ART may lower the incidence of HIV and, eventually, the prevalence of HIV on a community or population level.[9-11]

Two large, randomized controlled trials addressed the optimal time to initiate ART—START[12] and TEMPRANO.[13] Both studies demonstrated reductions in morbidity and mortality among individuals with HIV who had CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 and who were randomized to receive ART immediately when compared to individuals who delayed initiation of ART.

Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining conditions and certain serious non-AIDS–defining conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm^3 do not achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART,[14,15] and they have a shorter life expectancy than those who initiated therapy at higher CD4 count thresholds.[14-16]

Fundamental to the recommendation for earlier initiation of ART in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some individuals, the diagnosis of HIV is not made until the later stages of the disease. In a survey conducted between 2016 and 2017, it was noted that fewer than 40% of American adults had ever had an HIV test.[17] Evidence shows that many people with HIV access health care years before their HIV diagnosis but are not offered HIV testing despite recommendations from the Centers for Disease Control and Prevention (CDC) for routine testing for everyone aged 13 to 64 years.[18,19] There are also economic benefits to early diagnosis, including prolonging life, improving the quality of life, and decreasing the costs related to the management of AIDS and its co-morbidities.[20,21] Additionally, HIV screening is a key step in the Ending the HIV Epidemic initiative to prevent the transmission of HIV to others.[22]

Diagnosis of HIV is delayed more often in nonwhite individuals, those who inject drugs, those who live in rural communities, and older adults, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[23-25] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current CDC recommendations is essential. The U.S. Preventative Services Task Force recommends HIV testing for persons aged 15 to 65 years and for all pregnant individuals. HIV testing should also be performed for younger and older persons when indicated. This recommendation has been designated a Grade A recommendation by the U.S. Preventative Services Task Force, meaning that third-party payers should cover this service without cost to patients.[26] It is critical that everyone who receives an HIV diagnosis be educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. In order for both individuals with HIV and their sexual partners to fully benefit from early diagnosis, clinicians should initiate ART as soon as possible and provide support to enhance retention in care and ART adherence (see Adherence to the Continuum of Care).

Initiating Antiretroviral Therapy

ART is recommended for all individuals with HIV to reduce the morbidity and mortality associated with HIV infection **(AI)** and to prevent HIV transmission to sexual partners and infants **(AI)**. ART should be initiated as soon as possible after HIV diagnosis **(AII)**. When initiating ART, it is important to educate patients about the goals and benefits of ART and to identify and address barriers to care engagement and treatment adherence **(AIII)**. Patients should also understand that currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely without interruption. Initiating ART early is particularly important for patients with AIDS-defining conditions, those with acute or recent HIV infection, and individuals who are pregnant; delaying therapy in these subpopulations has been associated with high risks of morbidity, mortality, and HIV transmission.

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

Since individuals may fail to engage in care between the initial HIV diagnosis (or first clinic visit) and the time ART is prescribed, some groups have proposed rapid ART initiation on the same day of HIV diagnosis as a strategy to increase ART uptake and engagement in care and to accelerate the time to ART-mediated viral suppression. Rapid ART initiation also has the potential to reduce the time during which people with newly diagnosed HIV can transmit HIV. The rapid ART initiation strategy is supported by randomized controlled trials that were performed in resource-limited settings outside of the United States[27-29] and observational trials in the United States that included both immediate initiation of ART (on the day of diagnosis)[30-32] and rapid ART initiation (within days or weeks of diagnosis).[32,33] The results from some of these studies are discussed below.

A randomized controlled trial conducted in South Africa enrolled 377 individuals who had recently received HIV diagnoses (median CD4 count was 210 cells/mm^3). Participants were randomized to receive ART on the day of diagnosis or to receive the usual care (three to five additional visits over 2–4 weeks before ART initiation). Those who received immediate ART were significantly more likely to be virally suppressed at 10 months (64% vs. 51% of patients achieved viral suppression, respectively).[27] In another randomized controlled trial conducted in Haiti, a higher proportion of participants who were randomized to receive same-day ART initiation were retained in care and had viral suppression at the end of 1 year than those who initiated ART at the standard time (3 weeks after HIV testing); survival was also higher in the same-day ART initiation group.[28] A novel randomized controlled trial in Lesotho compared same-day, home-based ART to usual care and standard clinic referral (which involved a minimum of two counseling sessions prior to ART initiation). Participants randomized to receive same-day ART initiation were significantly more likely to achieve linkage to care within 90 days after enrollment (68.6% vs. 43.1%) and virologic suppression at

approximately 12 months (50.4% vs. 34.3%).[29]

There are many differences between health care in southern Africa and Haiti and in the United States—including differences in the health care systems, structural barriers to engagement in care, underlying HIV and tuberculosis (TB) epidemics, and ART regimens used—that limit the generalizability of the findings of the results from the studies described above. These studies, however, suggest that same-day initiation of ART is feasible and could potentially improve clinical outcomes.

While no randomized controlled trials have been conducted in the United States, several prospective observational studies have demonstrated the feasibility of same-day ART initiation. City-wide implementation of the San Francisco RAPID program among 225 patients who were newly diagnosed with HIV showed a median time from HIV diagnosis to ART start of 0 days (with a range of 0–56 days) and a median time from ART initiation to viral suppression (defined as <200 copies/mL) of 41 days. Over a median follow-up of 1.09 years (range 0–3.92 years), 92.1% of patients achieved virologic suppression. The RAPID study included a diverse and traditionally marginalized population, with a substantial proportion of participants having a major substance use disorder (51.4%), a major mental health disorder (48.1%), or unstable housing (30.6%).[31]

Whether rapid ART initiation improves long-term care engagement and virologic suppression is not yet known. One cohort study from France, however, found that earlier initiation of ART was negatively associated with care engagement at 1 year.[34] It should be emphasized that ART initiation on the same day of HIV diagnosis is resource intensive, and this strategy may require additional staff, multidisciplinary coordination, provision of ART starter packs, and consolidation of "usual care" patient services (e.g., clinical evaluation, education, counseling, initiation or optimization of insurance coverage, intake laboratory testing) into a 2- or 3-hour visit.[31] While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, removing structural barriers in order to facilitate rapid ART initiation may improve outcomes in the United States. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends initiating ART at the time of diagnosis (when possible) or soon afterwards to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, and improve the rate of virologic suppression among individuals who have recently received HIV diagnoses **(AII)**. This rating for this recommendation reflects the fact that only observational trials have been conducted in the United States or other highly resourced countries, where health systems and socioeconomic contexts differ substantially from those in the countries where randomized trials were conducted.

Antiretroviral Therapy for Persons with Acute Opportunistic Infections and Malignancies

Initiation of ART in the setting of an acute, AIDS-associated opportunistic infection (OI) or malignancy can improve immune function and potentially enhance treatment success for the OI. Clinicians should refer to the Adult and Adolescent Opportunistic Infection Guidelines for a more in-depth discussion on specific OIs. Below is a list of important factors to consider when initiating ART in these situations.

- **When no effective therapy exists for the OI (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy):** In these situations, ART may be the only treatment that can improve immune function and clinical outcomes. ART should be initiated without delay in these patients (see the Adult and Adolescent Opportunistic Infection Guidelines for more information).
- **Concerns regarding immune reconstitution inflammatory syndrome (IRIS):** For some OIs, such as cryptococcal and TB meningitis, immediate ART initiation may increase the risk of serious IRIS. A short delay before initiating ART may be warranted.[35-38] After ART initation, the patient should be closely monitored for signs and symptoms associated with IRIS.
- **Non-meningeal TB:** In these patients, initiating ART during treatment for TB confers a significant survival advantage;[39-43] therefore, ART should be initiated as recommended in Tuberculosis/HIV Coinfection.
- **For patients with mild to moderate cutaneous Kaposi sarcoma:** Prompt initiation of ART alone without

chemotherapy has been associated with improvement of cutaneous Kaposi sarcoma lesions, even though initial transient progression of Kaposi sarcoma lesions as a manifestation of IRIS can also occur.[44]

- **For patients with malignancies that require chemotherapy:**
  - A diagnosis of malignancy should not delay initiation of ART, nor should initiation of ART delay treatment for the malignancy.
  - Although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,[45] ART-mediated viral suppression is associated with longer survival among individuals undergoing treatment for AIDS-related lymphoma.[46]
  - Drug interactions should be considered when selecting ART, as there is the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some ritonavir-boosted or cobicistat-boosted regimens).

Evidence Supporting the Benefits of Antiretroviral Therapy in Preventing Morbidity and Mortality

Randomized Controlled Trials of Early vs. Deferred Antiretroviral Therapy

Two large randomized controlled trials, START and TEMPRANO, provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 count **(AI)**. The results of these two studies are summarized below.

START was a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART initiation in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. The study began at a time when initiating ART was not recommended until an individual's CD4 count fell below 350 cells/mm^3. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm^3 were randomized to initiate ART at randomization (early initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm^3 or until they developed a clinical indication for therapy (deferred initiation arm).

The study enrolled 4,685 participants, with a mean follow-up of 3 years. The primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events per 100 person-years) who were randomized to initiate ART early, and 96 participants (4.1%, or 1.38 events per 100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART; 95% confidence interval [CI], 0.30–0.62, $P < 0.001$). The most common clinical events reported were TB and malignancies (including both AIDS and non-AIDS malignancies). The majority of clinical events (59%) in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm^3, evidence for a benefit of initiating ART even before CD4 count declines below this threshold. Furthermore, the benefit of early ART was consistent across all participant subgroups, including gender, age, plasma HIV RNA levels, and income level of country. Although START was not sufficiently powered to compare the benefits of early ART initiation and deferred ART initiation for each category of clinical events, the benefit appeared to be particularly strong for AIDS events (HR 0.28), TB (HR 0.29), malignancies (HR 0.36), and severe bacterial infections (HR 0.39). The benefit at lower CD4 counts was primarily a reduction in the number of AIDS events, while the benefit at higher CD4 counts was primarily a reduction in the number of serious non-AIDS events. Importantly, early ART initiation also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61).[12,47]

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm^3 and who did not meet the criteria for starting ART according to World Health Organization guidelines at that time were randomized to start ART early (upon enrollment) or defer ART based on the national guidelines criteria for starting treatment. Half of the participants in each group received isoniazid for prevention of TB for 6 months and half did not. The primary study endpoint was a combination of all-cause deaths, AIDS diseases,

non-AIDS malignancies, and non-AIDS invasive bacterial diseases.

More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 counts >500 cells/mm^3, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower among those who were randomized to start ART early than among those in the deferred arm, with an HR of 0.56 in favor of early ART (95% CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART initiation is beneficial in reducing the rate of these clinical events.[13]

The TEMPRANO and START trials had very similar estimates for the protective effect of ART among individuals with HIV who had CD4 counts >500 cells/mm^3, further supporting the Panel's recommendation that ART be initiated in all patients regardless of CD4 count.

Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

A randomized clinical trial[3] and several large observational cohort studies[4-6] have provided strong evidence that achieving sustained viral suppression prevents sexual transmission of HIV. Thus, a key goal of ART is to prevent transmission of HIV to seronegative sexual partners **(AI)**. All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with ART prevents sexual transmission of HIV to their partners **(AII)**. Patients may recognize this concept as Undetectable = Untransmittable, or U=U. The results of these studies are summarized in Antiretroviral Therapy to Prevent Sexual Transmission of HIV.

Prevention of Perinatal Transmission

The first well-established example of ART reducing the risk of HIV transmission is the use of ART during pregnancy to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing the risk of perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, the use of combination ART during pregnancy has reduced the rate of perinatal HIV transmission from approximately 20% to 30% to 0.1% to 0.5%.[7,8] ART is thus recommended for all pregnant individuals with HIV, for both maternal health and for the prevention of HIV transmission to the newborn. In ART-naive pregnant individuals, ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy. All pregnant individuals should be tested for HIV upon confirmation of pregnancy, with testing repeated throughout pregnancy as needed for those at risk of HIV acquisition (see Maternal HIV Testing and Identification of Perinatal HIV Exposure in the Perinatal Guidelines).

Considerations When Initiating Antiretroviral Therapy

The ART regimens that are currently recommended as initial therapy in these guidelines (see What to Start) can suppress and maintain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have a low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

Optimizing Adherence, Antiretroviral Therapy Access, and Care Engagement

The key to successfully maintaining viral suppression is continuous access to ART and adherence to the prescribed regimen. Lack of adherence or intermittent access to ART can result in treatment failure and the emergence of drug resistance mutations that may compromise future treatment options. While optimizing adherence and linkage to care and ensuring continuous access are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier.[48] It is important to

discuss strategies to optimize adherence, care engagement, and ART access with all patients.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, substance use disorder, unstable housing, unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in Adherence to the Continuum of Care. However, mental illness, substance use disorder, and psychosocial challenges are not reasons to withhold ART from a patient. Rather, these issues indicate the need for additional interventions to support adherence, and they may influence the ART regimen that is recommended (see What to Start).

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as elite HIV controllers.[49,50] There are limited data on the benefits of initiating ART in these individuals. The START and TEMPRANO studies demonstrated that initiating ART is clearly beneficial for the patient regardless of CD4 count; therefore, delaying ART to see if a patient becomes an elite controller is **strongly discouraged**. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years.

Given that ongoing HIV replication occurs even in elite controllers, ART is strongly recommended for controllers with evidence of HIV disease progression, which is defined by declining CD4 counts or the development of HIV-related complications **(AIII)**. Nonetheless, even elite controllers with normal CD4 counts show evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS–related diseases.[49,51-53] One observational study suggested that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[54] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[55] Whether this potential immunologic benefit of ART in elite controllers outweighs the potential risks of ART toxicity and results in clinical benefit is unclear. Unfortunately, it is unlikely that randomized controlled trials will be able to address this question, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART initiation regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population.[56] Nevertheless, there is a clear rationale for prescribing ART to elite controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.

Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel's recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART initiation that are similar to those observed in adults. Compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression.[57] In recent years, more adolescents have been prescribed once-daily regimens, which has increased the rate of viral suppression in this population, even though there has been no significant difference in treatment adherence.[58] Because youth often face psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to receiving care and to adherence.

To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support to adolescent patients (see Adolescents and Young Adults with HIV).[59]

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Antiretroviral Therapy to Prevent Sexual Transmission of HIV (Treatment as Prevention) (Last updated December 18, 2019; last reviewed December 18, 2019)

Panel's Recommendations

- All persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) of <200 copies/mL, including any measurable value below this threshold value, with antiretroviral therapy (ART) prevents sexual transmission of HIV to their partners. Patients may recognize this concept as Undetectable = Untransmittable or U=U **(AII)**.
- Persons with HIV who are starting ART should use another form of prevention with sexual partners (e.g., condoms, pre-exposure prophylaxis [PrEP] for the HIV-negative sexual partner, sexual abstinence) for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII)**. Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual HIV transmission **(AIII)**.
- When the viral load is ≥200 copies/mL, additional methods are needed to prevent transmission of HIV to sexual partners until resuppression to <200 copies/mL has been confirmed **(AIII)**.
- Persons with HIV who intend to rely upon ART for prevention need to maintain high levels of ART adherence **(AIII)**. They should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII)**.
- At each visit for HIV care, clinicians should assess adherence to ART and counsel patients regarding the importance of ART to their own health as well as its role in preventing sexual HIV transmission **(AIII)**.
- Providers should inform patients that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other sexually transmitted infections (STIs) **(AII)**.
- Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral therapy (ART) not only reduces morbidity and mortality for persons with HIV but has now been definitively shown to prevent sexual transmission of the virus when the plasma HIV RNA (viral load) is consistently suppressed to <200 copies/mL, which includes any measurable viral load that is lower than this threshold value. Providers who manage patients with HIV need to be aware of the data supporting treatment as prevention (TasP, which persons with HIV may recognize as Undetectable = Untransmittable or U=U), its implications, and how to operationalize this prevention strategy in clinical practice. For persons with HIV who intend to rely on TasP for HIV prevention, providers should make an individualized assessment of the person's risk tolerance, personal health, history of maintaining viral suppression on treatment, and access to health care services and ART, as well as other factors that may affect their ability to maintain a high level of adherence to ART.

Evidence that Viral Load Suppression Prevents Sexual HIV Transmission

Suppressing the HIV viral load to <200 copies/mL with ART prevents sexual transmission of HIV. Observational data collected in the early 1990s from heterosexual couples demonstrated that sexual transmission from untreated persons with HIV was rare at viral loads of <1,000 copies/mL to 1,500 copies/mL and that the risk of transmission increased in dose-response fashion with increasing viral load.[1,2] Additional reports[3-7] and a meta-analysis[8] supported the observation that sexual HIV transmission risk in heterosexual persons was correlated with plasma viral load, and transmission was infrequent below the lowest limits of quantification for the viral load assays used at the time.

The first prospective clinical trial designed specifically to address this question was HPTN 052,

which randomized people with HIV who were in mixed HIV status couples (previously referred to as serodiscordant couples) to initiate ART early or to delay initiation. Initial results from this study were reported in 2011,[9] with final results reported in 2016.[10] The 2016 analysis reported that no phylogenetically linked sexual transmissions of HIV occurred among 1,763 couples who were followed a median of 5.5 years while the person with HIV was on ART and had a viral load <400 copies/mL for at least 6 months. Notably, four phylogenetically linked infections occurred within the 90 days after the partner with HIV had started ART and was presumably not yet virally suppressed, and four others occurred after the partner with HIV had experienced virologic failure. There were also a number of transmission events that were not phylogenetically linked, indicating acquisition from someone other than the enrolled study index partner.[11] HPTN 052 was conducted almost exclusively among heterosexual couples that lived in Africa and Asia and did not track the number or type of sexual exposures. In addition, ART was used as an adjunct to a comprehensive prevention package that provided condoms and encouraged condom use, as well as frequent testing for HIV and other sexually transmitted infections (STIs).

Three prospective observational studies—PARTNER 1,[12] PARTNER 2,[13] and Opposites Attract[14]—provided data from more diverse populations of mixed HIV status couples in which condomless sex was common. Clinical follow-up in these studies closely mimicked that of routine clinical care. Conducted in 14 European countries (PARTNER 1 and PARTNER 2) as well as Australia, Thailand, and Brazil (Opposites Attract), the investigators followed 548 heterosexual and 1,481 male-male mixed HIV status couples that engaged in 144,631 episodes of condomless vaginal or anal sex while the partner with HIV had a suppressed viral load on ART, defined as <200 copies/mL. In these studies, no phylogenetically linked transmissions were observed; however, as in HPTN 052, there were numerous non-phylogenetically linked transmissions attributed to partners outside the enrolled study couple relationship.

Integrating the Principles of Treatment as Prevention into Clinical Care

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends that providers inform all persons with HIV that maintaining an HIV viral load <200 copies/mL with ART prevents sexual transmission of HIV **(AII)**. This information may help motivate patients and help relieve stigma that can be a barrier to getting tested and entering into care, starting and remaining adherent to ART, and ultimately achieving and maintaining a viral load <200 copies/mL.[15] Although PARTNER 1, PARTNER 2, and Opposites Attract were designed to follow patients in the study as they would be typically be followed in clinical care for HIV, the participants reported high levels of ART adherence at study entry and many reported at least 1 year of condomless sex with an established sexual partner without transmission. As the principles of TasP are integrated into the clinical management of people with HIV who are on ART, implementation research will be critical to maximize the effectiveness of TasP in practice.

Frequency of Viral Load Assessment

The Panel has issued recommendations for viral load monitoring to manage the health of persons with HIV (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring). However, current data are insufficient to determine whether these recommendations represent the optimal monitoring schedule for the purpose of preventing sexual transmission of HIV. In the PARTNER studies and Opposites Attract, viral loads were generally assessed every 3 to 6 months during study follow-up, usually during the course of regular HIV care. Pending further data, the Panel recommends no change to the existing recommendations for monitoring viral load (see Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring) **(BII)**.

Time to Adequate Suppression after Starting Antiretroviral Therapy

A subgroup analysis from the Partners PrEP Study provided data regarding the risk of HIV transmission during and after the first 6 months on ART for the partner with HIV.[16] This analysis included 1,573 heterosexual East African couples in which the partners without HIV were randomized to the placebo arm

of the Partners PrEP Study and were tested monthly for HIV while the viral load of the partner with HIV was assessed every 6 months. Three phylogenetically linked infections were diagnosed in the 6 months prior to the first follow-up visit for the partners with HIV. The observed incidence rate of 1.79 per 100 person-years during this initial 6-month period after the partner with HIV started ART was slightly less than the 2.08 per person-years incidence rate observed in couples in which the person with HIV was not receiving ART. Viral suppression in this study was defined as <40 copies/mL, and the three infections were diagnosed at 0 days, 56 days, and 149 days after the partner with HIV started ART. After the partners with HIV had been taking ART for ≥6 months, no further transmissions were observed.

At this time, the Panel recommends that persons with HIV who are starting ART use another form of prevention with sexual partners for at least the first 6 months of treatment and until a viral load of <200 copies/mL has been documented **(AII)**. Many experts would recommend confirming sustained suppression before assuming that there is no further risk of sexual transmission of HIV **(AIII)**.

Adherence to Antiretroviral Therapy

Adherence to ART is paramount for persons who intend to prevent HIV transmission by achieving and maintaining a suppressed viral load. Viral rebound typically occurs within days to weeks after ART cessation and has been observed as early as 3 to 6 days after stopping treatment.[17-29] The minimum level of adherence that is required to prevent sexual transmission has not been determined and may vary depending on the ART regimen. In the key studies that defined the efficacy of TasP, adherence levels prior to study entry and during follow-up were very high. In clinical practice, most people who start ART will achieve a viral load <200 copies/mL within 6 months, but once this viral load is achieved, maintaining viral suppression can be a challenge, especially for those who have difficulty accessing ART and other HIV care. The Centers for Disease Control and Prevention (CDC) estimates that during 2015, 60% of persons with HIV and 78% of persons engaged in clinical care had viral loads <200 copies/mL at their most recent assessment.[30] Observational cohort data have demonstrated that within the first year of starting ART, up to 10% of persons with HIV can experience loss of viral suppression; however, the likelihood of maintaining a suppressed viral load generally improves over time. After a few years, 5% or fewer of persons on ART may experience loss of viral suppression.[31,32]

The Panel recommends that persons with HIV who intend to rely upon TasP be made aware of the need for high levels of ART adherence **(AIII)**. The Panel further recommends that adherence be assessed and counseling be provided at each visit for HIV care to reinforce the importance of adherence for the individual's health as well as its role in preventing HIV transmission **(AIII)**. Patients should be informed that transmission is possible during periods of poor adherence or treatment interruption **(AIII)**.

Adherence can be especially challenging for certain groups of patients, such as adolescents and young adults, homeless persons, persons with active substance use disorder, and persons who are involved with the criminal justice system. Recommendations to help manage and maximize ART adherence can be found in Adherence to the Continuum of Care. Persons for whom there is concern about adherence also merit counseling on how to properly use other prevention methods, especially barrier methods that prevent STIs.

Managing Transient Viremia, or "Blips"

Highly adherent patients may experience intermittent or transient viremia, commonly termed "viral blips." Blips are defined in the context of effective treatment as a single, measurable HIV RNA level, typically <200 copies/mL, that is followed by a return to a viral load below the limit of detection or quantification. With contemporary ART regimens, about 10% of persons per year who are adherent to ART may experience a blip.[33-35] Most blips likely represent normal biological fluctuation (i.e., variation around a mean undetectable viral load) or laboratory artifact and not inadequate adherence.[36-38] Persistent viremia ≥200 copies/mL has been associated with increasing risk of virologic failure[33,39] that, in the context of TasP, can lead to increased risk of sexual transmission.[10] The PARTNER studies and Opposites Attract excluded observation time when the viral load of

the participant with HIV was ≥200 copies/mL. The frequency of blips <200 copies/mL was not reported in Opposites Attract; however, in PARTNER 1 and PARTNER 2, transient elevations in viral loads above the limit of detection (50 copies/mL in these studies) but <200 copies/ml were observed for 6% and 4% of the total follow-up time, respectively, during which time no phylogenetically linked infections were observed.

One of the clinical challenges with blips is that they can only be defined retrospectively once the viral load has returned to a suppressed value. The Panel recommends that when the viral load is ≥200 copies/mL, persons with HIV and their sexual partners should use another form of prevention (e.g., condoms, pre-exposure prophylaxis for sexual partners without HIV, sexual abstinence) to protect against HIV transmission until a viral load <200 copies/mL is achieved **(AII)**. This recommendation applies both to persons who are starting ART (as noted earlier) and to those who have been taking ART and have achieved viral suppression but develop viral loads ≥200 copies/mL.

In cases where a patient achieves resuppression to <200 copies/mL after a detectable viral load ≥200 copies/mL, or when a patient with a viral load <200 copies/mL switches regimens (e.g., for regimen simplification or to avoid certain side effects), providers should check the viral load per recommendations in Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression **(AIII)**. There are presently no data to guide how long, if at all, a person might need to continue to use another form of prevention in these two circumstances. Individualized assessment is recommended based on the length and quality of adherence and time with viral load <200 copies/mL preceding the viral load ≥200 copies/mL.

Effect of Sexually Transmitted Infections on Treatment as Prevention

The presence of STIs in a person with HIV does not appear to meaningfully alter the risk of sexual transmission when the person's viral load is <200 copies/mL. The PARTNER studies and the Opposites Attract study regularly assessed participants for STIs, which were diagnosed in 6% of heterosexual participants and 13% to 27% of men who have sex with men. Although the authors of the studies noted that their findings could not rule out the possibility that STIs in participants with viral loads <200 copies/mL might affect the risk of HIV transmission, when viewed collectively, these data suggest that any effect is very small, since STIs were common and no linked infections were observed. The Panel recommends that patients using TasP be informed that maintaining a viral load of <200 copies/mL does not prevent acquisition or transmission of other STIs, and that it is not substitute for condoms or behavioral modifications **(AII)**. Providers should also routinely screen all sexually active persons with HIV for STIs, both for their own health and to prevent transmission of STIs to others **(AIII)**. Refer to CDC's Sexually Transmitted Diseases Treatment Guidelines for details.

Treatment as Prevention Applies Only to Sexual Transmission of HIV

Available clinical data only support the use of TasP to prevent sexual HIV transmission in patients with viral loads <200 copies/mL. The effectiveness of this strategy to prevent transmission from blood exposure (e.g., through nonsterile drug injection) has not been determined. In addition, while suppression of maternal viral load substantially reduces the risk of perinatal transmission and transmission through breastfeeding, it does not eliminate these risks, and transmission has occurred via breastfeeding despite continuous viral suppression (refer to the Perinatal Guidelines for details).

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What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).
- Data also support the use of the two-drug regimen, dolutegravir plus lamivudine, for initial treatment.
- Before initiating antiretroviral therapy (ART) in a person of childbearing potential, a pregnancy test should be performed **(AIII)**. Before prescribing ART to a person of childbearing potential, please refer to Table 6b for information about safety of different INSTI-based regimens taken around the time of conception.
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as *Recommended Initial Regimens for Most People with HIV* (in alphabetical order):
  - Bictegravir/tenofovir alafenamide/emtricitabine **(AI)**
  - Dolutegravir/abacavir/lamivudine—**only** for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection **(AI)**
  - Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)[a] **(AI)**
  - Dolutegravir/lamivudine **(AI)**—except for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
  - Raltegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF])[a] (**BI** for TDF, **BII** for TAF)
- To address individual patient characteristics and needs, the Panel also provides a list of *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a).
- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 9 highlights the advantages and disadvantages of different components in a regimen.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] TAF and TDF are two forms of tenofovir that are approved by the Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Introduction

More than 30 antiretroviral (ARV) drugs in seven mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These seven classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, and a CD4 T lymphocyte (CD4) post-attachment inhibitor. In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir (EVG).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 count increases in

most persons with HIV.[1-3] Additional data now support the use of the two-drug regimen dolutegravir (DTG) plus 3TC for initial treatment of people with HIV.[4]

Supporting Evidence and Rationale Used for the Panel's Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by drug manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen produces high rates of viral suppression, increases CD4 count, and has a favorable safety profile to be the strongest evidence on which to base recommendations. Comparative clinical trials of initial treatments generally show no significant differences in HIV-related clinical endpoints or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include medications approved by FDA based on bioequivalence or relative bioavailability studies demonstrating that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s) that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies in which a medication in an initial regimen that suppressed patients' viral loads is replaced by a new medication from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen's ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. In this section of the guidelines, the definition of an evidence rating of **II** is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, post-marketing safety data, observational cohort data published in peer-reviewed publications, and the experience of clinicians and community members who are actively engaged in patient care.

The Panel reviewed the available data to arrive at two regimen classifications for ARV-naive patients: (1) *Recommended Initial Regimens for Most People with HIV* and (2) *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a). *Recommended Initial Regimens for Most People with HIV* are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that, in certain clinical situations, other regimens may be preferred; these options are included in Table 6a in the category of *Recommended Initial Regimens in Certain Clinical Situations*. Examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous are outlined in Table 7.

There are many other ARV regimens that are effective for initial therapy but have disadvantages when compared with the regimens listed in Table 6a. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These other regimens are no longer included in Table 6a. A person with HIV who has a suppressed viral load and is not experiencing any adverse effects while on a regimen that is not listed in Table 6a need not necessarily change to one that is listed in the table. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

Regimens and medications listed in Table 10 below are not recommended as initial therapy. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables presented below and at the end of these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–9 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 10 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

- On the basis of 96-week data from the GEMINI-1 and GEMINI-2 trials showing that the efficacy of the two-drug regimen DTG plus 3TC is similar to that of the three-drug regimen DTG plus TDF/FTC,[4] the Panel has added DTG/3TC as one of the regimens *Recommended for Initial Treatment of Most People with HIV* (except for individuals with HIV RNA >500,000 copies/mL, hepatitis B virus (HBV) coinfection, or in whom antiretroviral therapy (ART) is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available).
- In the previous version of these guidelines, because of preliminary data raising concern that DTG use around the time of conception may be associated with an increased risk of infant neural tube defects (NTDs),[5] the Panel recommended against the use of DTG during the first trimester of pregnancy and in those of childbearing potential who are trying to conceive or who are sexually active and not using effective contraception. Now, additional results have shown that the prevalence of infant NTDs in association with DTG exposure at conception is lower than shown in the preliminary data[6,7] but still higher than with non-DTG containing regimens. These updated findings led to revisions in the Panel's recommendation for individuals of childbearing potential. Clinicians should review recommendations in Table 6b before prescribing INSTIs to these patients.
- The Panels' changes to the list of *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a) include the following:
  - Efavirenz (EFV) 400 mg/TDF/3TC has been added based on additional data on the regimen's efficacy **(BI)**.[8]
  - Raltegravir (RAL) plus ABC/3TC and lopinavir/ritonavir (LPV/r) plus 3TC have been removed because other regimens have advantages or more supporting data than these (relatively) less commonly used options.
- Table 7, which outlines clinical situations in which certain medications may be particularly advantageous, has been updated and revised.
- Data from studies showing increased weight gain with particular ARV medications, including some INSTIs and TAF, and especially in certain patient populations (i.e., women, Black people, and Hispanic people), are summarized.
- The section Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal has been updated. DTG/3TC is the preferred regimen because it has the most robust clinical data among the two-drug options in this situation.
- The discussions on clinical trial and safety data in the sections on INSTIs, NRTIs, NNRTIs and PIs have been updated.
- Given the growing number of FDA-approved generic ARV medications, cost and access are increasingly important factors to consider when choosing an ARV regimen (see Cost Considerations and Antiretroviral Therapy).

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 1 of 2)

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order. Table 7 provides ARV recommendations based on specific clinical scenarios.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC —**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] TAF and TDF are two forms of TFV approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 2 of 2)

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, BIC/TAF/FTC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/3TC, DTG/ABC/3TC, EFV (400 mg or 600 mg)/TDF/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TFV = tenofovir; TDF = tenofovir disoproxil fumarate

Table 6b. Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy for Persons of Childbearing Potential

Background:

- Preliminary data from a study in Botswana suggested that there is an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.[5,9] Updated results have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower (0.3%) than reported in the preliminary data, but still higher than in infants who were exposed to ART that did not contain DTG (0.1%).[6,7]
- It is not yet known whether use of other INSTIs around the time of conception also poses a risk of NTDs (i.e., a class effect).
- There are insufficient data to determine whether use of BIC around the time of conception and during pregnancy is safe.
- There is limited data on RAL use around the time of conception. Thus far, based on data collected from the Antiretroviral Pregnancy Registry, the drug manufacturer, and in a cohort study from the United States and other countries, no case of NTD has been reported.[10-12] Among those receiving RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[10-12]

Before Initiating an INSTI-Containing Regimen in a Person of Childbearing Potential:

- A pregnancy test should be performed **(AIII)**.
- To enable individuals of childbearing potential to make informed decisions, providers should discuss the benefits and risks of using DTG around the time of conception, including the low risk of NTDs and the relative lack of information on the safety of using other commonly prescribed ARV drugs, including other INSTIs, around the time of conception **(AIII)**.
- **For individuals who are trying to conceive,** the Panel recommends initiating one of the following regimens, which are designated as *Preferred* regimens during pregnancy in the Perinatal Guidelines: RAL, ATV/r or DRV/r plus TDF/FTC, TDF/3TC, or ABC/3TC. DTG would be an *Alternative*, rather than a *Preferred*, option **(BII)**.
- **For individuals who are not planning to conceive but who are sexually active and not using contraception**, consider a regimen's effectiveness and tolerability, the available data on potential teratogenicity, and the person's preferences (e.g., low pill burden) when choosing among regimens recommended for initial therapy (Table 6a). In this situation, DTG would be an *Alternative*, rather than *Preferred*, option **(BII)**. If the person becomes pregnant, changes to the ARV regimen may be warranted. Clinicians should refer to the Perinatal Guidelines for recommendations.
- **For individuals who are using effective contraception**, a DTG-based regimen is one of the recommended options; however, clinicians should discuss the risks and benefits of using DTG with patients to allow them to make an informed decision **(AIII)**.
- An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.
- EVG/c **should not be used during pregnancy** because of inadequate drug concentrations in the second and third trimesters **(AII)**.
- Clinicians should refer to the Perinatal Guidelines when prescribing ART for a pregnant person with HIV.

***Rating of Recommendations**: A = Strong; B = Moderate; C = Optional*

***Rating of Evidence:** I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; RAL = raltegravir; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

The goal of ART is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control. Initial therapy should be with two NRTIs combined with an INSTI, the combination of DTG/3TC or, in some individuals, a combination including two NRTIs plus an NNRTI or an RTV- or COBI-boosted PI. When selecting a regimen for a person with HIV, a number of patient- and regimen-specific characteristics should be considered. Some of the factors can be grouped into the categories listed below and may influence the choice of recommended regimens listed in Table 6a or the decision to consider alternative regimens. Table 7 includes recommendations for additional regimens to use in specific clinical scenarios.

Initial Characteristics to Consider in All Persons with HIV:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 count
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs.
- HLA-B*5701 status. Those who are HLA-B*5701 positive should not receive ABC. Regimens that do not include ABC can be initiated if HLA-B*5701 test results are not yet available; see Table 7 for regimens to initiate.
- Individual preferences
- Anticipated adherence to the regimen
- Timing of ART initiation after diagnosis (i.e., immediate versus delayed)

Note that results of pretreatment HIV RNA, CD4 count, and resistance testing do not need to be available before starting ART. See Table 7 for regimens to initiate if these results are not available.

Presence of Specific Conditions:

- Comorbid conditions: Cardiovascular disease; hyperlipidemia; renal disease; liver disease; osteopenia, osteoporosis, or other conditions associated with bone mineral density (BMD) loss; psychiatric illness; neurologic disease; drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or potential to become pregnant: Clinicians should refer to Table 6b and the Perinatal Guidelines for more detailed recommendations on the safety and effectiveness of ARV drugs during conception and throughout pregnancy.
- Coinfections: HBV, hepatitis C virus, tuberculosis (TB)

Regimen-Specific Considerations:

- Regimen's barrier to resistance
- Potential adverse effects and drug toxicities, including risk for development of comorbid diseases.
- Known or potential drug interactions with other medications (see Drug-Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination [FDC] or single-tablet regimen [STR] formulations, food requirements)

- Cost and access (see Cost Considerations and Antiretroviral Therapy)

General Considerations for INSTI-, PI-, or NNRTI-Based Regimens

The choice between an INSTI, PI, or NNRTI in an initial ARV regimen should be guided by the ARV drug's efficacy, barrier to resistance, and adverse effects profile; convenience; the patient's comorbidities and concomitant medications; and the potential for drug-drug interactions (see Tables 7 and 9).

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People with HIV* as listed in Table 6a include one of three INSTIs (BIC, DTG, or RAL) plus two NRTIs or DTG/3TC. For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations.[13-15] The Panel now recommends a two-drug regimen of DTG/3TC for initial therapy if certain criteria are met. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was noninferior to a three-drug regimen of DTG plus TDF/FTC. No treatment-emergent resistance was seen in either the two-drug or the three-drug group. The study inclusion criteria limited enrollment to participants with HIV RNA levels <500,000 copies/mL; no known major NRTI, PI, or NNRTI resistance; and without active hepatitis B.[4,16]

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance and lower pill burden than RAL-containing regimens. However, RAL-containing regimens may be preferred for individuals who wish to become pregnant (see Table 6b for further discussion). Treatment-emergent resistance has been reported very rarely in individuals receiving three-drug DTG-based therapy[17-19] and has not been reported in those receiving BIC-based regimens. In addition, transmitted resistance to BIC and DTG is rare. Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens may be considered for patients who plan to start ART before resistance test results are available (e.g., with rapid initiation of ART after diagnosis). BIC-based regimens have been shown to be noninferior to DTG-based regimens in clinical trials.[20,21]

Recent studies have shown that the prevalence of infant NTDs in association with DTG exposure at conception is still higher than with non-DTG containing regimens (0.3% vs. 0.1%, respectively).[6,7] For individuals of childbearing potential who are trying to conceive, DTG would be an *Alternative*, rather than a *Preferred*, option, as recommended in the Perinatal Guidelines. Clinicians should review the revised Table 6b before prescribing ART to a person of childbearing potential.

There are now data suggesting greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. The clinical significance of these findings is still unknown.[22-26] EVG-based regimens have the advantage of also being available as STRs and are recommended for certain clinical situations (see Table 7). However, EVG-based regimens have the potential disadvantages of a lower barrier to resistance than DTG- or BIC-containing regimens and, importantly, a greater potential for drug interactions because EVG is combined with COBI, a strong cytochrome P (CYP) 3A4 inhibitor.

Protease Inhibitor-Based Regimens

PK-enhanced PI-based regimens are recommended in certain clinical situations. Similar to elvitegravir/cobicistat (EVG/c), they carry the disadvantage of greater drug interaction potential than other ARV drugs. For those individuals in whom ART needs to begin urgently before resistance test results are available, boosted DRV may be an appropriate choice because the rate of transmitted PI resistance is low and boosted DRV has a high barrier to resistance and a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is available as an STR. Boosted ATV, like boosted DRV, has relatively few metabolic adverse effects in comparison to older boosted-PI regimens; however, ATV/r had a higher rate of adverse effect-associated drug discontinuation than darunavir/ritonavir (DRV/r) or RAL in a randomized clinical trial.[13] In a substudy of this

trial, and in a separate cohort study, atazanavir/ritonavir (ATV/r) use was associated with slower progression of atherosclerosis, as measured by carotid artery intima medial thickness.[27,28] Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and LPV/r) and an increased risk of cardiovascular events; however, this association was not seen with ATV.[29-34] Further study is needed.

NNRTI-Based Regimens

NNRTI-based regimens (which include doravirine [DOR], EFV, or rilpivirine [RPV]) may be options for some patients, although these drugs, especially EFV and RPV, have low barriers to resistance. The emergence of resistance at the time of virologic failure has also been reported with DOR. EFV has a long track record of widespread use, is considered safe in persons of childbearing potential, and has minimal PK interaction with rifamycins, making it an attractive option for patients who require TB treatment. EFV-based regimens (using either 400 mg or 600 mg dosing) have excellent virologic efficacy,[35] including in patients with high HIV RNA (except when EFV is used with ABC/3TC); however, the relatively high rate of central nervous system (CNS)-related side effects reduces the tolerability of EFV-based regimens. As an STR, EFV 600 mg is available with TDF/FTC or TDF/3TC; EFV 400 mg is available with TDF/3TC. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs that also include TAF/FTC or TDF/FTC, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with baseline HIV RNA levels >100,000 copies/mL and CD4 counts <200 cells/mm^3. DOR is available both as a single-drug tablet to be used with two NRTIs and as part of an STR with TDF/3TC. In randomized trials, DOR was noninferior to both EFV and DRV/r when either of these drugs were taken in combination with two NRTIs.[36,37] DOR has CNS tolerability advantages over EFV and more favorable lipid effects than DRV/r and EFV. DOR also has fewer potential drug interactions than EFV or RPV, and unlike with RPV, the virologic efficacy of DOR is not compromised in patients with high HIV RNA levels and low CD4 counts.

Regimens When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

In those patients in whom ABC, TDF, or TAF cannot be used or are not optimal, there are several two-drug options that do not contain these agents. Two-drug options **should not be used** in individuals with HBV coinfection or known pre-existing resistance to either ARV in the combination. Among the two-drug regimens, DTG/3TC is preferred because there are substantial data for this combination in initial therapy, with the caveat that people with HIV RNA >500,000 copies/mL were excluded from the largest trial.[4,16] Another two-drug treatment option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination should only be used in those with baseline CD4 counts >200 cells/mm^3 and HIV RNA levels <100,000 copies/mL.[38] A small, randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to once-daily DRV/r plus TDF/3TC, although this study has yet to be published.[39]

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 1 of 4)

This table guides clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a person with HIV, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a person is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 9 for additional information regarding the advantages and disadvantages of particular ARV medications. **Before initiating an INSTI-based regimen in a person of childbearing potential, review Table 6b for considerations in choosing the regimen.**

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	A higher rate of virologic failure has been observed in those with low pretreatment CD4 counts.
	HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL)	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels
	HIV RNA >500,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL • DTG/3TC	For DTG/3TC, limited data are available in patients above this viral load threshold.
	HLA-B*5701 positive or result unknown	**Do not use ABC-containing regimens.**	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
	ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly.	**Avoid NNRTI-based regimens and DTG/3TC.** **Avoid ABC.** **Recommended ART Regimens:** • BIC/TAF/FTC • DTG plus (TAF or TDF)[a] plus (3TC or FTC) • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance.
ART-Specific Characteristics	A one-pill, once-daily regimen is desired	**STR Options as Initial ART Include:** • BIC/TAF/FTC • DOR/TDF/3TC • DRV/c/TAF/FTC • DTG/ABC/3TC • DTG/3TC • EFV/TDF/FTC • EFV/TDF/3TC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use DTG/ABC/3TC if patient is HLA-B*5701 positive. DTG/3TC **is not recommended** if HIV RNA is >500,000 copies/mL. Do not use DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection or unknown HBV status. Do not use RPV-based regimens if HIV RNA is >100,000 copies/mL and CD4 count is <200/mm^3. See Appendix B, Table 10 for ARV dose recommendations in the setting of renal impairment.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 2 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics, continued	Food effects	**Regimens that Can be Taken Without Regard to Food:** • BIC-, DOR-, DTG-, or RAL-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens that Should be Taken with Food: • ATV/r- or ATV/c-based regimens • DRV/r- or DRV/c-based regimens • EVG/c/TAF/FTC[a] • EVG/c/TDF/FTC[a] • RPV-based regimens	Food improves absorption of these regimens. RPV-containing regimens should be taken with ≥390 calories of food.
		Regimens that Should be Taken on an Empty Stomach: • EFV-based regimens	Food increases EFV absorption and may increase CNS side effects.
Presence of Other Conditions	Chronic kidney disease (defined as CrCl <60 mL/min)	**In general, avoid TDF.** ABC may be used if patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). TAF may be used if CrCl >30 mL/min or if patient is on chronic hemodialysis (only studied with EVG/c/TAF/FTC). Consider avoiding ATV. **ART Options When ABC, TAF, or TDF Cannot be Used:** • DTG/3TC (if HIV RNA <500,000 copies/mL and without HBV coinfection) • DRV/r plus 3TC • DRV/r plus RAL (if CD4 count >200 cells/mm^3 and HIV RNA <100,000 copies/mL)	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 10 for specific dosing recommendations. TAF has less impact on renal function and lower rates of proteinuria than TDF. ATV has been associated with chronic kidney disease in some observational studies. ABC has not been associated with renal dysfunction.
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 10 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Osteoporosis	**Avoid TDF.**[a] ABC may be used if patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, **do not use** ABC/3TC plus (EFV or ATV/r).	TDF is associated with decreases in BMD along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF[a] and ABC are associated with smaller declines in BMD than TDF.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 3 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.** Patients on INSTI-based regimens who have pre-existing psychiatric conditions should be closely monitored. Some ARVs are contraindicated, and some psychiatric medications need dose adjustments when coadministered with certain ARVs.	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.
	HIV-associated dementia (HAD)	**Avoid EFV-based regimens if possible.**	The beneficial effects of ART on HAD-symptoms may be confounded by EFV-related neuropsychiatric effects.
	Medication-assisted treatment for opioid use disorder	Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring is recommended, as medications used to treat opioid dependence may need to be adjusted in some patients.	EFV reduces methadone concentrations and may lead to withdrawal symptoms. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations.
	Cardiac QTc interval prolongation	Consider avoiding EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.	High EFV or RPV concentrations may cause QT prolongation.
	High cardiac risk	Consider avoiding ABC- and LPV/r -based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen. Refer to Hyperlipidemia below for regimens associated with more favorable lipid profiles.	An increased risk of CV events with ABC has been observed in some studies. Observational cohort studies reported an association between some PIs (DRV, IDV, FPV, and LPV/r) and an increased risk of CV events; this risk has not been seen with ATV (see text). Further study is needed. Certain ART regimens are associated with more favorable lipid profiles than other regimens, although evidence on whether this improves CV outcomes is lacking.
	Hyperlipidemia	**The Following ARV Drugs Have Been Associated with Dyslipidemia:** • PI/r or PI/c • EFV • EVG/c BIC, DOR, DTG, RAL, and RPV have fewer lipid effects. TDF lowers lipids; therefore, switching from TDF to TAF is associated with increased lipids.	TDF has been associated with lower lipid levels than ABC or TAF.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 4 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care	Consider using regimens with a boosted PI or BIC or DTG.	These regimens have a high genetic barrier to resistance.
	Pregnancy	Refer to Table 6b and the Perinatal Guidelines for further guidance on ARV use during pregnancy.	
	Patients of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception	Refer to Table 6b for further guidance.	
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC **If TDF and TAF Are Contraindicated:** • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug that is active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	
	Treating TB disease with rifamycin antibiotics (rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug-drug interaction tables (Tables 21a-e) and TB/HIV Coinfection for information on ARV use with rifamycin antibiotics.	Rifamycin antibiotics are inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV.

[a] TAF and TDF are two FDA-approved forms of TFV. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BID = twice daily; BMD = bone mineral density; COBI = cobicistat; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HAD = HIV-associated dementia; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; UGT = uridine diphosphate glucuronosyltransferase

Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

The following sections provide detailed information on ARV drugs that the Panel recommends for initial therapy for persons with HIV, including the drugs' characteristics and adverse effects profiles, results from related clinical trials, and Panel recommendations on their use.

Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy-Naive Patients

Characteristics	ABC/3TC	3TC[a]	TDF/3TC	TAF/FTC	TDF/FTC
Dosing Frequency	Once daily	Once daily	Once daily	Once daily	Once daily
Available Coformulations for ART-Naive Patients	• ABC/3TC • DTG/ABC/3TC	DTG/3TC	• TDF/3TC • DOR/TDF/3TC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC	• TAF 25 mg/FTC • BIC/TAF 25 mg/FTC • DRV/c/TAF 10 mg/FTC • EVG/c/TAF 10 mg/FTC • RPV/TAF 25 mg/FTC	• TDF/FTC • EFV/TDF/FTC • EVG/c/TDF/FTC • RPV/TDF/FTC
Adverse Effects	**ABC:** • HSR to ABC is associated with the presence of HLA-B*5701 allele. • Increase in CV events is associated with ABC use in some, but not all, cohort studies.	See below	**TDF:** • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.	**TAF:** • Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF) • Decrease in BMD (less than with TDF; similar to with ABC)	**TDF:** • Renal insufficiency, proximal renal tubulopathy • Decrease in BMD • Renal and bone toxicity are exacerbated by pharmacologic boosters.
	3TC: No significant adverse effects			**FTC:** Skin discoloration	
Other Considerations	**ABC:** • Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list. **3TC:** • Epivir HBV™ is for the treatment of HBV and contains a different dose of 3TC than the formulation for ART. Thus, Epivir HBV™ should not be used for HIV treatment. • Coadministration of 3TC with sorbitol-containing drugs decreases 3TC concentration and should be avoided.			FTC should not be used as sole treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.	
	3TC or ABC/3TC **should not be used** as treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.		Also used for HBV treatment. Discontinuation may precipitate HBV flare. See Appendix B, Table 10 for dose recommendations in patients with renal insufficiency.		

[a] 3TC is recommended for use with DTG in ART-naive persons, and with DRV/r if ABC, TDF, and TAF are not optimal. Otherwise, dual-NRTI backbones are recommended.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

FDA-approved NRTIs include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), ABC, TDF, TAF, 3TC, and FTC. Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States because of high rates of serious toxicities, including peripheral neuropathy and mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, lipoatrophy, and bone marrow suppression from ZDV use. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.[40,41]

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended as components of initial therapy. In addition, 3TC may be used as a single NRTI with DTG, or, in select circumstances, with boosted DRV. Table 6a provides recommendations and ratings for the individual regimens. These recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.[42] TAF is less likely to cause kidney and bone toxicities than TDF. TDF is associated with lower lipid levels than TAF. Safety, cost, and access are among the factors to consider when choosing between these drugs. ABC/3TC, TDF/3TC, and 3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug[43-45] (see also the discussion in the Dolutegravir section).[46]

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each combination was used with either EFV or ATV/r. In patients with baseline HIV RNA ≥100,00 copies/mL, the time to virologic failure was significantly shorter with ABC/3TC than with TDF/FTC, regardless of whether the third active drug was EFV or ATV/r.[43] In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in with once-daily LPV/r. Virologic efficacy was similar in the two study arms, including in a subgroup of participants with HIV RNA ≥100,000 copies/mL.[45]
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. At week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants than among TDF/FTC-treated participants.[44]

Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

An STR of DTG/3TC has now been approved as an initial ART regimen. Please refer to the INSTI section for full discussion.

GEMINI 1 and GEMINI 2 were identically designed randomized, double-blind clinical trials that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and estimated glomerular filtration rate (eGFR) ≥50 mL/min.[4,16]

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

- Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of EVG/c/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with eGFR ≥50 mL/min.
  - TAF/FTC was virologically noninferior to TDF/FTC at week 48 (92% vs. 90% of participants had plasma HIV RNA <50 copies/mL, respectively),[47] but TAF/FTC was superior to TDF/FTC at week 144 (84.2% vs. 80% of participants with plasma HIV RNA <50 copies/mL), largely driven by a

higher rate of treatment discontinuation in the TDF arm.[48]

- Participants in the TAF arm had significantly smaller reductions in BMD at the spine and hip than those in the TDF arm through 144 weeks.[48] Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through week 96.[49] Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at 96 weeks, with no change in total cholesterol to HDL ratio.[50]

- Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC each combination administered with boosted DRV in ART-naive participants:
  - A Phase 2 study of coformulated darunavir/cobicistat (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC in treatment-naive patients demonstrated similar virologic suppression rates in both arms (75% vs. 74%).[51] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
  - The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At 48 weeks, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[52]

- One analysis evaluated data from 11 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF and of TAF when either drug was taken with or without PK boosters (RTV or COBI). There were no significant differences between unboosted TDF and TAF in terms of virologic efficacy or in the number of participants who discontinued treatment because of renal or bone adverse events or fractures. However, bone- and renal-related toxicities were more pronounced when TDF was used with RTV or COBI.[42]
- To assess the ability of TAF to maintain HIV and HBV suppression, 72 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 $\log_{10}$ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[53] In this study, 96% of participants were on a TDF/FTC-containing regimen before the switch. Key results of the study showed that:
  - Among those who switched to EVG/c/TAF/FTC, HIV suppression was maintained in 94.4% and 91.7% of participants at 24 and 48 weeks, respectively. At 24 and 48 weeks, 86.1% and 91.7% of participants, respectively, had HBV DNA <29 $\log_{10}$ IU/mL.
  - Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.[53]

Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy

In alphabetical order.

Abacavir/Lamivudine (ABC/3TC)

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.[46,54-56]

Adverse Effects

Hypersensitivity Reactions:

- Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50% of HLA-B*5701-positive patients, if given ABC, will have a related HSR.[57,58] HLA-B*5701 testing should be done if the

use of ABC is being considered. A patient who tests positive for HLA-B*5701 should not be given ABC and ABC hypersensitivity should be noted on the patient's allergy list. Patients who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR **should never be rechallenged**, regardless of their HLA-B*5701 status.

Cardiovascular Risk:

- An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of an MI, particularly in participants with pre-existing cardiac risk factors.[30,59]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[60-66] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[29,67-70]
- An analysis of data from NA-ACCORD found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.[71]
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations:

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- ABC and 3TC are available separately and as a coformulated tablet in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in patients with renal dysfunction.

The Panel's Recommendations:

- ABC should only be prescribed for patients who are HLA-B*5701 negative.
- On the basis of clinical trial safety and efficacy data, experience in clinical practice, and the availability of DTG/ABC/3TC as an FDC, the Panel classifies DTG/ABC/3TC as a *Recommended Initial Regimen for Most People with HIV* **(AI)** (see the discussion of DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, atazanavir/cobicistat (ATV/c), DRV/c, DRV/r, or RAL is only recommended for patients with pretreatment HIV RNA levels <100,000 copies/mL. See Table 6a for more detailed recommendations on the use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

Lamivudine (3TC) as Single NRTI

3TC was approved for HIV treatment in 1995 and is often used in combination with ABC or TDF. Based on the GEMINI-1 and GEMINI-2 studies[4] that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive patients with HIV RNA <500,000 copies/mL, 3TC may be used as a single NRTI with DTG (for more information, please refer to INSTI section). In addition, based on the ANDES trial, if ABC, TDF, and TAF cannot be used, 3TC can be used as a single NRTI with DRV/r[39] (please refer to Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate

Cannot Be Used or Are Not Optimal.)

Adverse Effects:

- Long-term experience with 3TC has shown that it is well tolerated with no significant adverse effects.

Other Factors and Considerations:

- 3TC is available as an STR with DTG.
- 3TC has activity against HBV but is insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- There are two brand-name formulations of 3TC (one for HIV and the other for HBV), but doses are different. The dose for HIV treatment is 3TC 300 mg daily.
- The dose of 3TC should be adjusted in patients with creatinine clearance (CrCl) <50 mL/min.
- Sorbitol-containing drugs can decrease 3TC concentration and co-administration should be avoided.

The Panel's Recommendations:

- The Panel recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV* with three exceptions. DTC/3TC **is not recommended** for:
  - Individuals with HIV RNA >500,000 copies/mL;
  - Individuals with HBV coinfection or whose HBV status is unknown; *and*
  - Individuals starting ART before the results of genotypic resistance testing for reverse transcriptase are available.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

TAF, an oral prodrug of tenofovir (TFV), is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

Adverse Effects

Renal and Bone Effects:

- The potential for adverse kidney and bone effects is lower with TAF than with TDF. In randomized controlled trials that compared TAF and TDF in treatment-naive or virologically suppressed patients, TAF had more favorable effects on renal biomarkers and bone density than TDF (described below).

Lipid Effects:

- In randomized controlled trials in ART-naive patients, as well as in switch studies (described below), levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and those receiving TDF. The clinical significance of this finding is not clear.[47,72,73]

Weight Gain:

- Initiation of TAF in ART-naive individuals has been associated with greater weight gain than initiation of TDF[23,24] and ABC.[23] Significant weight gain was initially reported in a cohort of patients switching from TDF-containing to TAF-containing regimens.[74] In ADVANCE, an open-label trial conducted in

South Africa that compared EFV/TDF/FTC versus DTG plus TDF/FTC versus DTG plus TAF/FTC in ART-naive patients, there was a greater increase in body weight with initiation of TAF than with TDF.[24] Weight gain was most pronounced in black women (10 kg over 96 weeks). This is an area of intense investigation and the clinical significance of the effect is still uncertain. It is also unclear whether change of therapy results in reversal of weight gain.

Other Factors and Considerations:

- TAF/FTC is available in FDCs with bictegravir (BIC), DRV/c, EVG/c, or RPV, allowing the regimens to be administered as a single pill taken once daily with food.
- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see the INSTI section below).
- TAF-containing regimens are approved for patients with eGFR ≥30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in patients on hemodialysis with eGFR <15 mL/min.[75]
- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).[53]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[76] and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with BIC, DTG, and RAL.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) and Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC)

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.[77-86] In a 10-day, open-label, randomized, monotherapy trial that was not powered to find a difference between study arms, the reduction in viral load from baseline was 1.7 $\log_{10}$ for FTC 200 mg once daily and 1.5 $\log_{10}$ for 3TC 150 mg twice daily.[87] In a meta-analysis of 12 trials, there was no significant difference in treatment success between 3TC and FTC.[88] In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with an NNRTI (EFV or nevirapine [NVP])[89] or with a boosted PI.[90] TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis. However, it is noteworthy that the participants in the NNRTI cohort who were taking 3TC generally had higher viral loads, lower CD4 counts, and were more likely to be using injection drugs at the start of the study than those taking FTC.[89] There was no difference in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI.[90] A retrospective analysis of an Italian national database found that viral resistance was more common with TDF/3TC than with TDF/FTC, but this was not observed in clinical trials.[91]

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[92,93] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),[94] and pre-existing renal impairment.[95] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that the risk of renal dysfunction is greater when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers such as

proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.[93,95-99]

- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC with PK boosting.[42]

Bone Effects:

- While initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[100,101] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above).
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[102]
- Adverse bone outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that fractures and study discontinuations due to bone adverse events occured more frequently among patients who took TDF/FTC with PK boosting than among those who took TAF/FTC with PK boosting.[42]

Other Factors and Considerations:

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.
- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring). In patients who have pre-existing renal insufficiency (CrCl <60 mL/min),[103] use of TDF should generally be avoided. If TDF is used, a dose adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 10 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HBV/HIV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most persons with HIV when combined with DTG or RAL. See Table 6a for recommendations regarding use of TDF/FTC with other drugs.
- TDF should be used with caution or avoided in patients with renal disease and osteoporosis.
- When TDF is used, especially in conjunction with a PK booster, clinicians should monitor for renal and bone safety during therapy. Boosters should be avoided when possible in patients taking TDF.

Integrase Strand Transfer Inhibitor–Based Regimens

Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy-Naive Patients

Before starting an INSTI-based regimen in a person of childbearing potential, clinicians should refer to Table 6b for further guidance.

Characteristics	BIC	DTG	EVG	RAL
Dosing Frequency	Once daily	**Once Daily:** • In ART-naive or INSTI-naive persons **Twice Daily:** • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In INSTI-experienced persons with certain INSTI drug resistance mutations	Once daily; requires boosting with COBI	• 400 mg twice daily, *or* • 1,200 mg (two 600-mg tablets) once daily
STR Available for ART-Naive Patients	BIC/TAF/FTC	• DTG/ABC/3TC • DTG/3TC	• EVG/c/TAF/FTC • EVG/c/TDF/FTC	No
Available as a Single-Drug Tablet	No	Yes	No	Yes
Approved for ART-Experienced Patients	No	Yes, with twice-daily dosing for patients with certain INSTI drug resistance mutations	No, but sometimes used in combination with DRV and TAF/FTC as part of a simplification regimen in patients with resistance.	Yes, for patients with drug resistance mutations to RTV-boosted PIs or NNRTIs, but not to INSTIs
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available.	Yes, for some isolates; effective with DTG 50 mg twice-daily dose	No	No
Adverse Effects	Nausea, diarrhea (GI disturbance greater with EVG/c), headache, insomnia. Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than NNRTI or boosted PI regimens (see text). Depression and suicidality are rare, occurring primarily in patients with pre-existing psychiatric conditions.			
	↑ CPK (4%)	Hypersensitivity, hepatotoxicity, ↑ CPK, myositis	↑ TG, ↑ LDL	↑ CPK, myopathy, hypersensitivity, SJS/TEN
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)	EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor	No
Chelation with Polyvalent Cation Supplements and Antacids	Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 21d for recommendations regarding dosing separation of INSTIs and these drugs.			
Other Key Potential Drug Interactions	UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate	EVG is a UGT1A1 substrate; COBI is a P-gp inhibitor.	UGT1A1 substrate

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; INSTI = integrase strand transfer inhibitor; LDL = low density lipoprotein; MATE = multidrug and toxic compound extrusion; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; OAT = organic cation transporter; P-gp = p-glycoprotein; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; SJS/TEN = Stevens Johnson Syndrome/toxic epidermal necrolysis; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; UGT = uridine diphosphate glucuronosyltransferase

Summary

Four INSTIs—BIC, DTG, EVG, and RAL—are approved for use in ART-naive patients with HIV.

The Panel recommends one of the following INSTI-based regimens for most people with HIV:

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)**—if HLA-B*5701 negative
- DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF) with (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)
- DTG/3TC **(AI)**, except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Among the INSTI-based regimens, RAL-containing regimens have the longest clinical experience, and they have been shown to have durable virologic efficacy; however, they have a higher pill burden than BIC- and DTG-containing regimens. EVG and RAL have lower barriers to resistance than BIC and DTG. Because of its high barrier to resistance, DTG plus two NRTIs or BIC/TAF/FTC may be considered for patients who must start ART before resistance test results are available. EVG-based regimens require boosting with COBI, which results in a greater potential for interaction with concomitant medications, Therefore, EVG-based regimens are now considered *Recommended Initial Regimens in Certain Clinical Situations*.

All INSTIs are generally well tolerated, though there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have rarely been reported in patients receiving INSTI-based regimens.[104-107]

Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than NNRTI- or boosted PI-regimens.[23-26,108,109] In randomized trials of ARV-naive individuals, the mean increase in weight from baseline associated with BIC and DTG was similar and greater than with EVG/c.[23] Greater weight gain has also been observed after initiation of TAF,[20,23,24] or with a switch from TDF to TAF[74] especially in conjunction with INSTIs. While ARV-associated weight gain appears to disproportionately affect women, Blacks and Hispanics,[23,24,108,110] predictors and mechanism(s) for the weight gain are still unclear. Further questions that need to be clarified include regional distribution of the weight gain,[22] whether it is associated with significant cardio-metabolic risk,[111] and whether it is reversible upon discontinuation of the offending agent.

Preliminary data from an observational study in Botswana suggested that there may be an increased risk of NTDs in infants born to individuals who were receiving DTG at the time of conception.[5,9] Additional data show that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower than previously reported, but still higher than in infants exposed to non-DTG regimens.[6,7] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review the information in Table 6b.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen for Most People with HIV

Bictegravir (BIC)

BIC is an INSTI that is approved by FDA for initial therapy in adults with HIV as a component of a single-tablet, once-daily regimen with TAF and FTC.

Efficacy in Clinical Trials:

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary

efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at week 48.

- The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At week 96, 84% of participants in the BIC arm and 86% of those in the DTG arm achieved HIV RNA <50 copies/mL.[20]
- The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At week 96, 88% of participants in the BIC/TAF/FTC arm and 90% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL.[21]

Adverse Effects:

- BIC is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of any grade with an incidence ≥5% included diarrhea, nausea, and headache. Some studies have shown greater weight gain among people initiating INSTI-based regimens, particularly Black women. In a pooled analysis of eight randomized, controlled trials in ART-naive individuals, the weight gain at 96 weeks with BIC- and DTG-based regimens was similar (approximately 3.5 kg).[23]

Other Factors and Considerations:

- BIC is a CYP3A4 substrate and a UGT1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John's wort should also be avoided.[112]
- BIC is an inhibitor of the drug transporters OCT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, BIC is unlikely to affect the metabolism of medications that are CYP3A4 substrates.
- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids, or calcium or iron supplements). See the BIC product label for dosing recommendations when using BIC with these products.[112]
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are typically observed within the first 4 weeks of BIC therapy (with a median increase of 0.10 mg/dL after 48 weeks). This increase is comparable to that seen with other drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations, and BIC should not be used in these individuals until more data are available.
- There are insufficient data to determine whether use of BIC around the time of conception and during pregnancy is safe.

The Panel's Recommendation:

- On the basis of clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a *Recommended Initial Regimen for Most People with HIV* **(AI)**.
- Before prescribing BIC to a person of childbearing potential, review Table 6b. BIC should not be used in pregnancy because of insufficient safety data.

Dolutegravir (DTG)

DTG is an INSTI with a higher barrier to resistance than EVG or RAL. In ART-naive patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. DTG is given once daily, with or without food. Preliminary data from Botswana suggested that there may be an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception,[5,9] but additional data indicate the risk is lower than previously reported.[6,7] More detailed discussions of this potential risk and recommendations for the use of DTG are found below and in Table 6b.

Efficacy in Clinical Trials:

- The efficacy of DTG in ART-naive patients has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.

DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have shown virologic efficacy that is similar to BIC/TAF/FTC (see the discussion in the BIC section above).[20,21,113,114]
- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily. Each drug was administered in combination with an investigator-selected, two-NRTI combination (ABC/3TC or TDF/FTC) to 822 participants. At week 96, DTG was noninferior to RAL.[86]

DTG plus Two NRTIs versus EFV plus Two NRTIs:

- The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At week 48, DTG plus ABC/3TC was superior to EFV/TDF/FTC, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[46] At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[115]
- The ADVANCE trial, an open label, noninferiority trial conducted in South Africa, compared DTG with either TDF/FTC or TAF/FTC to EFV/TDF/FTC. At week 48, the DTG-based regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL. More participants discontinued the trial regimen in the EFV group than in the DTG group.[24]
- The NAMSAL ANRS 12313 study, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared DTG to EFV 400 mg, both combined with TDF/3TC. At week 48, DTG was noninferior to EFV 400 mg, with HIV RNA <50 copies/mL in 74.5% and 69.0% of participants in the DTG and EFV arms respectively.[8]

DTG plus Two NRTIs versus PI/r plus Two NRTIs:

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to DRV/r 800 mg/100 mg once daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 48, DTG was superior to DRV/r, with 90% and 83% of participants achieving HIV RNA <50 copies/mL, respectively. The rate of participants who discontinued their assigned regimen was higher in the DRV/r arm.[116] The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pretreatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.[117]
- The ARIA trial, an open-label, Phase 3b randomized controlled trial, compared the efficacy and safety of DTG/ABC/3TC to ATV/r plus TDF/FTC in ART-naive, nonpregnant women. At week 48, 82% of participants in the DTG group and 71% in the ATV group ($P = 0.005$) achieved HIV RNA viral loads <50

copies/mL. The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.[118]

DTG/3TC:

- In the GEMINI-1 and GEMINI-2 trials, 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC based on the proportion of participants with viral loads <50 copies/mL (86% in DTG plus 3TC group and 89.5% in DTG plus TDF/FTC group).[4] Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the rate of those with HIV RNA <50 copies/mL at week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failures in the two-drug group.
- Two other small, non-randomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.[119,120]

Adverse Effects:

- DTG is generally well tolerated. The most commonly reported adverse reactions of moderate-to-severe intensity were insomnia and headache. As discussed earlier, some studies have shown greater weight gain among people initiating INSTI-based regimens, including regimens with DTG.[23-26]
- Case series of neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.[104,105] Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs.[106,107] However, analyses of data from large randomized controlled trials and a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and other ARV regimens,[121] with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs,[122] not just DTG. Further studies will be needed to clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric adverse events has not been defined.
- An observational surveillance study of birth outcomes among pregnant women on ART in Botswana identified five cases of NTDs among infants born to 1,683 women (0.3%) who initiated a DTG-based regimen around the time of conception. The incidence of NTDs among infants born to women who were receiving other ARV drugs at the time of conception was 0.1%, although data were limited for all other ARV agents except EFV.[9] See Table 6b for recommendations on prescribing INSTIs as part of initial therapy, including for people of childbearing potential.
- Weight gain has been reported with INSTIs, including DTG, as discussed in the Summary of this INSTI section.

Other Factors and Considerations:

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment.
- DTG has fewer drug interactions than EVG/c. See Drug-Drug Interactions for specific drug-drug interactions that require dosage adjustment.

- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see Drug-Drug Interactions). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives are taken. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in patients receiving DTG as part of a three-drug regimen for initial therapy.[17-19] The incidence of resistance with DTG is much lower than with EVG or RAL, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel's Recommendations:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI)**, TAF/FTC **(AI)**, or TDF/(FTC or 3TC) **(AI)** as a *Recommended Initial Regimen for Most People with HIV*.
- The Panel also recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV* except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or of HBV testing are available.
- Individuals of childbearing potential should have a pregnancy test before initiating DTG **(AIII)**.
- A DTG-based regimen can be considered for individuals of childbearing potential who are using effective contraception after a discussion of the risks and benefits of the regimen so that individuals can make informed decisions (see Table 6b for details) **(BIII)**.
- For initial therapy of individuals of childbearing potential who are trying to conceive or are sexually active and not using contraception, please see Table 6b for recommendations.

Raltegravir (RAL)

RAL was the first INSTI approved for use in both ARV-naive and ARV-experienced patients.

Efficacy in Clinical Trials

RAL 400 mg Twice Daily plus Two NRTIs versus Comparator Drug plus Two NRTIs:

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label, randomized trial.
    - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[82] RAL was superior to EFV at 4 and 5 years,[85,123] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
    - The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.
    - The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads ≥100,000 copies/mL and 125 participants with baseline viral loads <100,000 copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, there was no difference in virologic response between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.[86]
    - ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens

that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the ritonavir-boosted protease inhibitor (PI/r) arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[13]

RAL 1,200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:

- In a Phase 3, randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1,200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each administered with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.[124]

Adverse Effects:

- RAL, when compared in a randomized trial to DRV/r or ATV/r, all with TDF/FTC, led to a greater mean increase in waist circumference.[125]
- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.[126]
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see the discussion under DTG).[121,127]

Other Factors and Considerations:

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients.
- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids **is not recommended**. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See Table 21d for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.
- Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[10-12] Data on RAL use around the time of conception is limited. Thus far, based on data collected from Antiretroviral Pregnancy Registry, the manufacturer and in a cohort study from the United States and other countries, no case of NTD has been reported.[10-12]

The Panel's Recommendations:

- On the basis of these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily plus TDF/FTC **(BI)** or TAF/FTC **(BII)** as a *Recommended Initial Regimen for Most People with HIV*.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen in Certain Clinical Situations

Elvitegravir (EVG)

EVG is available as a component of two STRs: EVG/c/TDF/FTC and EVG/c/TAF/FTC. COBI is a specific,

potent CYP3A inhibitor that has no activity against HIV. It acts as a PK enhancer of EVG, which allows for once-daily dosing of the combination but increases the likelihood of significant drug interactions.

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ART-naive participants has been evaluated in two randomized, double-blind active-controlled trials.
  - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.[128]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[129]
  - In a randomized, blinded trial that compared EVG/c/TDF/FTC to ATV/r plus TDF/FTC in women with HIV, EVG/c/TDF/FTC had superior efficacy, in part because of a lower rate of treatment discontinuation.[15]
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR ≥50 mL/min.[47,50]
  - At 48 and 96 weeks, TAF was noninferior to TDF when both drugs were combined with EVG/c/FTC; at 144 weeks, EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC.[48]

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[128,129]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[130]
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see the discussion under DTG).

Other Factors and Considerations:

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI is a PK enhancer, it is a CYP3A enzyme inhibitor, which may lead to significant interactions with medications that are metabolized by this enzyme (see Drug-Drug Interactions).[131]
- Administration of EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see Drug-Drug Interactions). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.[132] Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be closely monitored and evaluated for evidence of TDF-related proximal renal tubulopathy.[99]
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.[99]
- EVG/c/TAF/FTC **is not recommended** for patients with estimated CrCl <30 mL/min unless they are on chronic hemodialysis. An observational study of 55 people with HIV who were on hemodialysis suggested that EVG/c/TAF/FTC given once daily (after hemodialysis on dialysis days) can be used safely in persons with no resistance to any of the ARV drugs in this STR.[133]
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-

treated patients whose therapy failed.[128,129] These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.

- EVG/c **is not recommended** during pregnancy because of low drug exposure when taken during the second and third trimesters.[134]

The Panel's Recommendation:

- On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as *Recommended Initial Regimens in Certain Clinical Situations* **(BI)**. EVG/c/TAF/FTC should only be used in people with estimated CrCl ≥30 mL/min, unless they are on chronic hemodialysis. EVG/c/TDF/FTC should only be used in people with estimated CrCl ≥70 mL/min.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors that are Recommended for Antiretroviral Therapy-Naive Patients

Characteristics	DOR	EFV	RPV
Dosing Frequency	Once daily	Once daily	Once daily
Food Requirement	With or without food	On an empty stomach	With a meal
STR Available for ART-Naive Patients	DOR/TDF/3TC	• EFV 600 mg/TDF/FTC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC	• RPV/TAF/FTC • RPV/TDF/FTC
Available as a Single-Drug Tablet	Yes	Yes	Yes
Adverse Effects	Generally well tolerated	• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, somnolence • Skin rash • QTc prolongation	• Depression, headache • Skin rash • QTc prolongation
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate	CYP3A4 substrate, mixed inducer/inhibitor	CYP3A4 substrate
Other Significant Drug Interactions	None	CYP2B6 and 2C19 inducer	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug-Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids.

Key: 3TC = lamivudine; CNS = central nervous system; CYP = cytochrome P; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

Five NNRTIs (delavirdine [DLV], DOR, EFV, etravirine [ETR], NVP, and RPV) are currently approved by FDA for the treatment of HIV when used in combination with other ARV drugs.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) are the prevalence of NNRTI-resistant viral strains in ART-naive patients[135] and the drugs' low barrier for the development of resistance. Resistance testing should be performed before initiation of an NNRTI-based regimen in ART-naive patients. High-level resistance to

all NNRTIs (except ETR or DOR) may occur with a single mutation. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.[136,137] DOR-, EFV-, and RPV-based regimens are now categorized as *Recommended Initial Regimens in Certain Clinical Situations* for ART-naive patients.

Doravirine (DOR)

Efficacy in Clinical Trials

The efficacy of DOR-based therapy for treatment of HIV in ART-naive individuals was demonstrated in two randomized, double-blind, placebo-controlled trials.

DOR-Based Regimen versus EFV-Based Regimen:

- In DRIVE-AHEAD, 734 participants received either DOR/TDF/3TC or EFV/TDF/FTC, both as FDCs.[36]
    - At 48 weeks, DOR/TDF/3TC was noninferior to EFV/TDF/FTC, with 84.3% of participants who received DOR/TDF/3TC and 80.8% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Although virologic responses to ART overall were lower in participants with pre-ART HIV RNA >100,000 copies/mL, there was no difference between the DOR-treated and EFV-treated participants. Virologic responses overall were lower in participants with pre-ART HIV RNA >100,000 copies/mL, but there was no difference between the DOR and EFV groups.
    - A greater proportion of participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.3% vs. 2.7%). Neuropsychiatric side effects were more common in the EFV arm.
    - Genotype resistance results were reported for 13 participants with virologic failure in the DOR arm and 10 participants in the EFV arm. For the DOR arm, seven out of 13 participants had NNRTI resistance and five out of 13 had NRTI resistance; for EFV, nine out of 10 participants had NNRTI resistance and five out of 10 had NRTI resistance.
    - LDL cholesterol and non-HDL cholesterol did not change with DOR use, whereas both increased with EFV use.
    - At 96 weeks, 77.5% and 73.6% of participants in the DOR arm and the EFV arm had maintained HIV RNA <50 copies/mL, respectively.[138]

DOR-Based Regimen versus DRV/r-Based Regimen:

- In DRIVE-FORWARD, 769 participants received DOR or DRV/r once daily along with two investigator-selected NRTIs, either ABC/3TC or TDF/FTC.[37]
    - At 48 weeks, DOR was found to be noninferior to DRV/r when these drugs were administered with two NRTIs, with 84% of study participants receiving DOR versus 80% of those receiving DRV/r achieving HIV RNA <50 copies/mL at 48 weeks.
    - Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.
    - At week 96, DOR was superior to DRV/r in terms of virologic suppression,[139] with a higher rate of discontinuation in the DRV/r group.
    - Genotype resistance results were reported for seven and eight participants with virologic failure in the DOR and DRV/r arms, respectively. No drug resistance mutations were detected in either group.
    - Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol and triglycerides were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations:

- DOR is available as a single-drug, 100-mg tablet[140] and as part of an STR that contains DOR/TDF/3TC 100 mg/300 mg/300 mg[141] and is dosed once daily, with or without food.
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 21b). DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.[142]
- DOR-based regimens have not been directly compared to INSTI-based regimens in clinical trials.
- There are currently no data on the safety of DOR use during pregnancy.

The Panel's Recommendations:

- On the basis of the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC **(BI)** and DOR plus two NRTIs (**BI** for TDF/FTC and **BIII** for TAF/FTC) as *Recommended Initial Regimens in Certain Clinical Situations*.
- Because the number of clinical trial participants who received DOR plus ABC/3TC is much lower than the number who received TDF/FTC plus DOR, the Panel considers ABC/3TC plus DOR to be an option for initial therapy **(CI)**.

Efavirenz (EFV)

Efficacy of EFV 600 mg Daily Dose in Clinical Trials:

- Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. EFV-based regimens have demonstrated superiority or noninferiority to a number of comparator regimens in ART-naive patients in several randomized controlled trials.
- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[143]
- In the ECHO and THRIVE studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.[144]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[128]
- The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 48 weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.
- ADVANCE, an open label, noninferiority trial, compared TDF/FTC/EFV 600 mg to DTG combined with either TDF/FTC or TAF/FTC. At week 48, the DTG regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL. More participants in the EFV group than in the DTG group discontinued the trial regimen.[24]

In clinical trials, some regimens have demonstrated superiority to those with EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to an EFV regimen at the primary endpoint of viral suppression at week 48.[46]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks,[82] but RAL was superior to EFV at 4 and 5 years,[85,123] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label STaR trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.[145]

Efficacy of Low-Dose Efavirenz (EFV 400 mg Daily) in Clinical Trials:

- ENCORE 1, a multinational, randomized, placebo-controlled trial, compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg (reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.[35] While the frequency of overall adverse events was not different between groups, EFV-related adverse events and treatment-related discontinuations occurred less frequently in the EFV 400 mg group than in the EFV 600 mg group. Although there were fewer self-reported CNS events in the 400 mg group, the groups had similar rates of psychiatric events. The 400-mg dose of EFV is now approved in the United States for initial treatment of HIV infection and is coformulated with TDF and 3TC in an FDC tablet.
- NAMSAL ANRS 12313 (an open-label, multicenter randomized noninferiority trial) compared EFV 400 mg to DTG, both combined with TDF/3TC. At week 48, EFV 400 mg was noninferior to DTG based on percentage of participants with viral suppression to HIV RNA <50 copies/mL (69.0% in EFV group vs. 74.5% in DTG group).[8]
- In an open label trial, 25 pregnant women with HIV and HIV RNA <50 copies/mL while on an EFV-based regimen were switched from EFV 600 mg to EFV 400 mg daily (the TDF and FTC or 3TC components of the regimen did not change). Participants were monitored closely with EFV concentrations measured weekly and viral loads biweekly during pregnancy and postpartum. Stopping criteria were HIV RNA >50 copies/mL on two consecutive occasions or random EFV concentration <800 ng/mL on three consecutive occasions. All participants maintained viral load suppression to HIV RNA <50 copies/mL throughout the study.[146]
- A PK study enrolled 22 persons with HIV (without TB) who were on an EFV-based regimen and had HIV RNA levels <50 copies/mL. Participants were switched from EFV 600 mg to EFV 400 mg. Fourteen days after the switch, isoniazid and rifampin were started for 12 weeks. The combination resulted in only minimal reduction in EFV 400 mg PK parameters, which were within the range of concentrations seen in the ENCORE 1 trial. HIV RNA levels <50 copies/ mL were maintained in all participants during the study.[147]

Adverse Effects:

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use has also been associated with suicidality; however, evidence for this association has differed among various large studies. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (LPV/r, ATV, ATV/r, or ABC-based regimens).[148] Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behavior among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses.[149] This association, however,

was not found in analyses of three large observational cohorts[150,151] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[152] A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried a greater risk of suicidal ideation or depression than NVP.[153]

- Delayed onset neurotoxicities, including ataxia and encephalopathy, have been reported months to years after EFV use.[154,155]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[156,157] Consider an alternative to EFV in patients taking medications known to increase the risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.

Other Factors and Considerations:

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily FDC tablet that includes 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children weighing ≥35 kg.[158,159]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6, and therefore, may potentially interact with other drugs that use the same pathways (see Tables 21b, 22a, and 22b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.[160] A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).[161]
- People with HIV who are taking a regimen that includes EFV should be screened for depression and suicidality.

The Panel's Recommendations:

- Given the availability of regimens with fewer treatment-limiting adverse events and noninferior or superior efficacy, the Panel classifies EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC **(BI)** or EFV 600 mg plus TAF/FTC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- Randomized clinical trial data have demonstrated the noninferiority of EFV 400 mg compared to EFV 600 mg[35] and to DTG.[8] This dose has not been studied in a U.S. population. The Panel classifies EFV 400 mg/TDF/3TC as a *Recommended Initial Regimen in Certain Clinical Situations* **(BI)**.

Rilpivirine (RPV)

RPV is an NNRTI that is approved for use in combination with NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL.

Efficacy in Clinical Trials:

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.[144] At 96 weeks, the following findings were reported:
  - RPV was noninferior to EFV overall.
  - Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with virologic failure, NNRTI and NRTI resistance were more frequently identified in those treated with RPV.

- Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 counts <200 cells/mm^3 than in those with CD4 counts ≥200 cells/mm^3.
- STaR, a Phase 3b, open-label study, compared the FDCs of RPV/TDF/FTC and of EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks[162] were similar to those reported at 48 weeks.[145]
  - RPV was noninferior to EFV overall.
  - RPV was superior to EFV in patients with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among patients with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated patients than in EFV-treated patients.
  - There were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% vs. 1%, respectively).
- The STR of RPV/TAF/FTC was approved by FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF 25 mg in participants taking the coformulated drug were similar to those seen in participants who received RPV as the single-drug tablet and TAF/FTC as part of the STR of EVG/c/TAF 10 mg/FTC.[76]

Adverse Effects:

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer patients in the RPV arms discontinued therapy due to adverse events. However, up to 9% of clinical trial participants experienced depressive disorders, including approximately 1% of participants who had suicidal thoughts or who attempted suicide. Patients receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations:

- RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC and with TDF/FTC. Among available STRs, RPV/TAF/FTC is the smallest tablet.
- RPV/TAF/FTC and RPV/TDF/FTC are given once daily and must be administered with a meal (containing at least 390 kcal).
- RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for persons with HIV who have achieved viral suppression.[163] However, this combination has not been studied in ART-naive individuals, and it **is not recommended** for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is **contraindicated** in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see Drug-Drug Interactions for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug-Drug Interactions).
- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations:

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as *Recommended Initial Regimens in Certain Clinical Situations*.
- Use of RPV with TAF/FTC **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

Protease Inhibitor-Based Regimens

Table 8d. Characteristics of Protease Inhibitor Options that are Recommended for Antiretroviral Therapy-Naive Patients

Characteristics	ATV	DRV
Dosing Frequency	Once daily	• Once daily for PI-naive patients • Twice daily for PI-experienced patients with certain PI mutations
PK Boosting	PK-boosting with RTV or COBI is generally recommended. Unboosted ATV is also FDA-approved for ART-naive patients.	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	• ATV/c	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	• Jaundice • Indirect hyperbilirubinemia • Cholelithiasis • Nephrolithiasis • PR prolongation	• Skin rash • Increase in serum transaminases • Hyperlipidemia • A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate, inhibitor	CYP34A substrate, inhibitor
Other Significant Drug Interactions	ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 21a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.	N/A

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; N/A = not applicable; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

FDA-approved PIs include ATV, atazanavir/cobicistat (ATV/c), DRV, DRV/c, FPV, IDV, LPV/r, nelfinavir, RTV, saquinavir (SQV), and tipranavir. PI-based regimens with PK enhancement (also called boosting) have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance. Because transmitted PI resistance is uncommon, PI-based regimens are generally recommended if early ART initiation is necessary, before resistance test results are available. Few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with NNRTI-based regimens and some INSTI-based regimens.[164,165] For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy because of poor adherence. All PIs (boosted by either RTV or COBI) inhibit the CYP3A4 isoenzyme,

which may lead to significant drug-drug interactions (see Drug-Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of recommended PIs are listed in Table 9 and Appendix B, Table 5.

PI-based regimens that are recommended for use in ART-naive patients should have proven virologic efficacy, once-daily dosing, a lower pill count than older PI-based regimens, and good tolerability. On the basis of these criteria, the Panel considers once-daily DRV/r, DRV/c, ATV/c, or ATV/r, each administered in combination with with two NRTIs, as PI-based regimen options in the category of *Recommended Initial Regimens in Certain Clinical Situations*. DRV/c/TAF/FTC is now available as an STR. In a large, randomized controlled trial comparing DRV/r, ATV/r, and RAL, each administered in combination with TDF/FTC, all three regimens achieved similar virologic suppression rates; however, the proportion of patients who discontinued their assigned treatment because of adverse effects, mainly hyperbilirubinemia, was greater in the ATV/r arm than in the other two arms.[13]

Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[29-31,34] Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens than in those receiving other regimens.[33] Further study is needed.

Compared to other PIs, LPV/r, FPV/r, unboosted ATV, and SQV/r have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are no longer recommended as options for initial therapy.

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials:

- The ARTEMIS study compared DRV/r (800 mg/100 mg once daily) with LPV/r (800 mg/200 mg once daily or 400 mg/100 mg twice daily), both administered in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at week 48,[80] and superior at week 192.[166] Among participants with baseline HIV RNA levels >100,000 copies/mL, virologic response rates were lower in the LPV/r arm than in the DRV/r arm.
- The FLAMINGO study compared DRV/r with DTG, each administered in combination with two NRTIs, in 488 ART-naive participants. The rate of virologic suppression at week 96 was significantly greater among those who received DTG than in those who received DRV/r. The higher rate of virologic failure observed in the DRV/r group was primarily related to the great number of failures among those with a viral load >100,000 copies/mL, and secondarily because there were more drug discontinuations in the DRV/r group.[14]
- ACTG A5257, a large, randomized, open-label trial, compared ATV/r to DRV/r or RAL, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.[13]
- The DRIVE-FORWARD study compared DRV/r to DOR, both administered with two investigator-selected NRTIs, in ART-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR and 84% of participants who received DRV/r achieving HIV RNA levels <50 copies/mL.

Adverse Effects:

- Patients taking DRV/r may develop a skin rash, which is usually mild-to-moderate in severity and self-

limited. Treatment discontinuation is necessary on rare occasions when severe rash with fever or elevated transaminases occur.

- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[13] The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P \leq 0.02$).[167]
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.[34]

Other Factors and Considerations:

- DRV/r is administered once daily with food in treatment-naive patients.
- DRV has a sulfonamide moiety and should be used with caution in patients with severe sulfonamide allergies. In clinical trials, the incidence and severity of rash were similar in participants with and without a history of sulfonamide allergy. Most patients with sulfonamide allergy are able to tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, and this may lead to significant interactions with other medications metabolized through this same pathway (see Drug-Drug Interactions).

The Panel's Recommendations:

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with TDF/FTC **(AI)**, with TAF/FTC **(AII)**, or with ABC/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.

Darunavir/Cobicistat (DRV/c)

In a study in healthy volunteers, DRV 800 mg with COBI 150 mg was bioequivalent to DRV 800 mg with RTV 100 mg based on the maximum concentration and area under the concentration time curve for DRV.[168] Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that of DRV combined with RTV, bioequivalence for the C_{min} was not achieved.[169]

Efficacy in Clinical Trials:

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the STR DRV/c/TAF/FTC and DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of the study (91% and 88% had HIV RNA < 50 copies/mL, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group. In the DRV plus TAF/FTC arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.[52] At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL.[170]
- In a single-arm trial in which most of the patients were treatment-naive (94%), the coformulated DRV/c 800 mg/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.[171]

Adverse Effects:

- The most common drug-related adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.

Other Factors:

- DRV/c 800 mg/150 mg is available as a coformulated boosted PI or as an STR with TAF/FTC 10 mg/200 mg.

The Panel's Recommendations:

- The Panel recommends DRV/c plus TAF/FTC or TDF/FTC **(AI)** and DRV/c plus ABC/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situation*s.
- DRV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

Atazanavir/Ritonavir (ATV/r) or Atazanavir/Cobicistat (ATV/c)

Efficacy in Clinical Trials:

ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs

- The CASTLE study compared once-daily ATV/r (300 mg/100 mg) with twice-daily LPV/r (400 mg/100 mg), each administered in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.[172]

ATV/r plus Two NRTIs versus EFV plus Two NRTIs

- The ACTG A5202 study compared open-label ATV/r and EFV, each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.[143] In a separate analysis, women assigned to receive ATV/r were found to have a higher risk of virologic failure than women assigned to receive EFV or men assigned to receive ATV/r.[173]

ATV/r plus Two NRTIs versus INSTI plus Two NRTIs

- In a study that compared ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.[129] A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.[15] At week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm and five women in the INSTI arm discontinued therapy because of an adverse event.
- In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, the rate of virologic suppression (HIV RNA <50 copies/mL) in the DTG arm was noninferior to that in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.[118]

ATV/r plus Two NRTIs versus DRV/r plus Two NRTIs versus RAL plus Two NRTIs

- In ACTG A5257, a significantly higher proportion of patients in the ATV/r arm discontinued randomized treatment because of adverse events, mostly for elevated indirect bilirubin/jaundice or gastrointestinal toxicities. Lipid changes in participants in the ATV/r and DRV/r arms were similar. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[13]

ATV/c versus ATV/r plus Two NRTIs

- In the Gilead Study 114, all patients received TDF/FTC and ATV and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.[174] Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentage of adverse events that caused patients to discontinue treatment, and changes in serum creatinine and indirect bilirubin levels were comparable.[175]

Adverse Effects:

- The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.[176]

- Nephrolithiasis,[177-179] nephrotoxicity,[32] and cholelithiasis[180] have also been reported in patients who received ATV.
- Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

Other Factors and Considerations:

- ATV/c and ATV/r are dosed once daily and with food.
- ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly PPIs) may impair absorption of ATV. Table 21a provides recommendations for use of ATV/c or ATV/r with these agents.
- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug-Drug Interactions).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[29-31,34] Another study of an observational cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens than in participants receiving other regimens.[33] Further study is needed.

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC **(BII)** or TDF/FTC **(BI)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- ATV/c or ATV/r plus ABC/3TC is no longer included in the list of *Recommended Initial Regimens in Certain Clinical Situations*, because it has disadvantages when compared with other regimens in this category. In a randomized trial, when combined with ATV/r, ABC/3TC was less potent than TDF/FTC in people with HIV RNA >100,000 copies/mL;[43] in a separate randomized trial, ATV/r was not as well tolerated as DRV/r.[13]
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

Most currently recommended ARV regimens consist of two NRTIs plus a third active drug. In some clinical situations, it is preferable to avoid ABC, TAF, and TDF, such as in patients who are HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment. In this situation, DTC/3TC, which is recommended for most people with HIV, is the preferred option. In addition, several other NRTI-limiting two-drug regimens have been evaluated in clinical studies. Of note, two-drug regimens **should not be used** in people with HBV/HIV coinfection or during pregnancy. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of patients with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

Strategies Supported by Evidence from Clinical Trials

Dolutegravir/Lamivudine (DTG/3TC)

Among the two-drug regimens for initial therapy, the combination of DTG/3TC has the most clinical data supporting its use;[4,120,181] therefore, it is recommended over the other two-drug regimens listed below. Clinicians should refer to the INSTI section above for a summary of the data supporting the use of DTG/3TC as initial therapy for ART-naive people with HIV.

The Panel's Recommendation:

- The Panel recommends DTG/3TC as an initial regimen for most people with HIV **(AI)**; as such, this is the preferred regimen when use of ABC, TAF, or TDF is not optimal. DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available. Before prescribing DTG/3TC for a person of childbearing potential, review Table 6b for a discussion of important considerations.

Darunavir/Ritonavir plus Lamivudine (DRV/r plus 3TC)

- In the ANDES trial, 145 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.[39] The rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (91% and 92%, respectively).

The Panel's Recommendation:

- On the basis of results from a small study with a relatively short follow-up period, DRV/r plus 3TC can be considered for use in people who cannot take ABC, TAF, or TDF **(CI)**. Although the ANDES trial supports the use of DRV/r plus 3TC, it is smaller than other trials of NRTI-limiting regimens, and larger studies are warranted.

Darunavir/Ritonavir plus Raltegravir (DRV/r plus RAL)

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm^3, however, there were more virologic failures in the two-drug arm; a trend towards more failure was also observed among those with pretreatment HIV RNA ≥100,000 copies/mL.[38] High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.[182,183]

The Panel's Recommendation:

- On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

A Nucleoside-Limiting Regimen with Insufficient Supporting Data

Darunavir/Ritonavir plus Rilpivirine (DRV/r plus RPV)

- In a single-arm, open-label, pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or RPV received DRV/r plus RPV for 48 weeks. Half of the participants (18 of 36) had baseline HIV viral loads >100,000 copies/ml. By week 36, 97% of participants (35 of 36) achieved HIV RNA <50 copies/ml, and by week 48, all achieved viral suppression (HIV RNA <50 copies/ml).[184]

The Panel's Recommendation:

- At this time, the Panel **does not recommend** DRV/r plus RPV given the small sample size of the study described above and the lack of comparative data evaluating DRV/r plus RPV as initial therapy for people with HIV.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 5)

Note: All drugs within an ARV class are listed in alphabetical order.

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI Regimens	**ABC/3TC**	• Coformulated with DTG • Generic formulations are available for ABC/3TC, ABC, and 3TC.	• May cause life-threatening HSRs in patients who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, EVG/c, or RPV • Active against HBV; a recommended dual-NRTI option for patients with HBV/HIV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for patients with eGFR ≥30 mL/min • Can be used in patients with eGFR <30 mL/min and on chronic hemodialysis	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. **• Not recommended in pregnancy.**
	TDF/3TC	• Coformulated with DOR • Generic formulations are available for TDF, 3TC, TDF/3TC, and EFV/TDF/3TC. • Long-term clinical experience • Active against HBV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with lower lipid levels than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Single NRTI	**3TC**	• Coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, ABC	• DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
INSTI	**BIC**	• Coformulated with TAF/FTC • Higher barrier to resistance than EVG and RAL • No food requirement	• See Table 6b for considerations related to prescribing an INSTI-based regimen to people of childbearing potential. • Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • Inhibits tubular secretion of Cr without affecting glomerular function. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug-drug interactions. • **Should not be used in pregnancy** because of lack of data and coformulation with TAF. • See discussion in text regarding weight gain related to INSTIs.
	DTG	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC/3TC and 3TC • No food requirement • Minimal CYP3A4 interactions • Favorable lipid profile	• Data from Botswana suggest that DTG exposure during conception may be associated with risk of NTDs in the infant (0.3% vs. 0.1% with non-DTG ARV drugs). • See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, continued	**EVG/c**	• Coformulated with TDF/FTC or TAF/FTC • Compared with ATV/r, EVG/c causes smaller increases in total and LDL cholesterol. • EVG/c/TAF/FTC can be used in patients on chronic hemodialysis.	• See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in **significant interactions** with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Food requirement. • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • **Should not be used in pregnancy** because of low drug exposure. • See discussion in text regarding weight gain related to INSTIs.
	RAL	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions • Favorable lipid profile	• See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe HSRs (including SJS and TEN) have been reported. • Higher pill burden than other INSTI-based regimens. • No FDC formulation. • Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.
NNRTI	**DOR**	• Coformulated with TDF/3TC • Compared to EFV, fewer CNS side effects • No food requirement • Favorable lipid profile	• Shorter-term clinical experience than with EFV and RPV. • Potential for CYP450 drug interactions (see Tables 21b, 22a and 22b). • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
NNRTI, continued	**EFV**	• EFV 600 mg is coformulated with TDF/FTC and TDF/3TC. • EFV 400 mg is coformulated with TDF/3TC. • EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA. • EFV 400 mg has fewer CNS side effects than EFV 600 mg. • EFV 600 mg can be given with rifamycin antibiotics (rifampin, rifabutin, or rifapentine).	• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Late onset ataxia and encephalopathy have also been reported. • Periodic screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV. • Dyslipidemia • Rash • QTc interval prolongation; consider using an alternative to EFV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes. • Transmitted resistance is more common than with PIs and INSTIs. • Greater risk of resistance at the time of treatment failure than with PIs. • Potential for CYP450 drug interactions (see Tables 21b and 22a). • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities).

	RPV	• Coformulated with TDF/FTC and TAF/FTC
		• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs
		• Compared with EFV:
		  • Fewer CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• **Not recommended** in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3 because of higher rate of virologic failure in these patients.
			• Depression and suicidality
			• QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.
			• Rash
			• Transmitted resistance is more common than with PIs and INSTIs.
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.
			• Potential for CYP450 drug interactions (see Tables 21b and 22a).
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption.
			  • **Contraindicated** with PPIs.
			  • Use with H2 antagonists or antacids with caution (see Table 21a for detailed dosing information).

PIs	**ATV/c** or **ATV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs. • ATV/c and ATV/r have similar virologic activity and toxicity profiles. • Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion. • Individual ATV and RTV components are available as generics.	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 21a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 21a).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 5 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs, continued	**ATV/c** Specific considerations	Coformulated tablet	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI **is not recommended** in pregnancy because of low drug levels.
	DRV/c or **DRV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs.	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 21a). • Increased CV risk reported in one observational cohort study. • Hepatotoxicity has been reported, especially in those with pre-existing liver disease.
	DRV/c Specific considerations	• Coformulated as DRV/c and DRV/c/TAF/FTC	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI **is not recommended** in pregnancy because of low drug levels.

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase

Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Coformulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC/3TC/ZDV plus TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T plus 3TC	• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)
ddI plus 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities, such as pancreatitis and peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including SJS and TEN) • When compared to EFV, NVP did not meet noninferiority criteria
PIs	
ATV (Unboosted)	• Less potent than boosted ATV
DRV (Unboosted)	• Use without RTV or COBI has not been studied
FPV (Unboosted) or **FPV/r**	• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV • Less clinical trial data for FPV/r than for other RTV-boosted PIs
IDV (Unboosted)	• Inconvenient dosing (3 times daily with meal restrictions) • Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
IDV/r	• Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
LPV/r	• Higher pill burden than other PI-based regimens • Higher RTV dose than other PI-based regimens • GI intolerance
NFV	• Inferior virologic efficacy • Diarrhea
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity

Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
PIs, continued	
SQV (Unboosted)	• Inadequate bioavailability • Inferior virologic efficacy
SQV/r	• High pill burden • Can cause QT and PR prolongation; requires pretreatment and follow-up ECG
TPV/r	• Inferior virologic efficacy • Higher rate of adverse events than other RTV-boosted PIs • Higher dose of RTV required for boosting than other RTV-boosted PIs
Entry Inhibitors	
T-20 Fusion Inhibitor	• Only studied in patients with virologic failure • Twice-daily subcutaneous injections • High rate of injection site reactions
IBA CD4 Post-Attachment Inhibitor	• Only studied in a very small number of patients with virologic failure • Requires IV therapy • High cost
MVC CCR5 Antagonist	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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What Not to Use (Last updated October 17, 2017; last reviewed October 17, 2017)

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

Antiretroviral Drugs Not Recommended

The following ARV drugs are no longer recommended for use because of suboptimal antiviral potency, unacceptable toxicities, high pill burden, or pharmacologic concerns: delavirdine (DLV), didanosine (ddI), indinavir (IDV), nelfinavir (NFV), and stavudine (d4T).

Antiretroviral Regimens Not Recommended

Monotherapy

Nucleoside reverse transcriptase inhibitor (NRTI) monotherapy is inferior to dual-NRTI therapy.[1] Protease inhibitor (PI) monotherapy is inferior to combination antiretroviral therapy (ART).[2-6] Integrase strand transfer inhibitor (INSTI) monotherapy has resulted in virologic rebound and INSTI resistance **(AI)**.[7,8]

Dual-NRTI Regimens

These regimens are inferior to triple-drug combination regimens **(AI)**.[9]

Triple-NRTI Regimens

Triple-NRTI regimens have suboptimal virologic activity[10-12] or a lack of data **(AI)**.

Antiretroviral Components Not Recommended

Atazanavir plus Indinavir

Both PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly **(AIII)**.

Cobicistat plus Ritonavir as Pharmacokinetic Enhancers

This combination may be prescribed inadvertently, which may result in additive CYP3A4 enzyme inhibition and may further increase the concentrations of ARV drugs or other concomitant medications (see Tables 21a and 21d).

Didanosine plus Stavudine

The combination of ddI and d4T can result in peripheral neuropathy, pancreatitis, and lactic acidosis, and it has been implicated in the deaths of several pregnant women **(AII)**.[13]

Didanosine plus Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) increases ddI concentrations,[14] serious ddI-associated toxicities,[15,16] immunologic nonresponse,[17] early virologic failure,[18,19] and resistance[18,20] **(AII)**.

Two Non-Nucleoside Reverse Transcriptase Inhibitor Combinations

Excess clinical adverse events and treatment discontinuation were reported in patients randomized to receive treatment with two non-nucleoside reverse transcriptase inhibitors (NNRTIs).[21] Efavirenz (EFV) and nevirapine (NVP) are enzyme inducers, and both of these drugs can reduce concentrations of etravirine (ETR) and rilpivirine (RPV) **(AI)**.[22]

Emtricitabine plus Lamivudine

Both drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo* **(AIII)**.[23]

Etravirine plus Unboosted Protease Inhibitor

ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established **(AII)**.[22]

Etravirine plus Fosamprenavir/Ritonavir

ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established **(AII)**.[22]

Etravirine plus Tipranavir/Ritonavir

Tipranavir/ritonavir (TPV/r) significantly reduces ETR concentrations **(AII)**.[22]

Nevirapine Initiated in ARV-Naive Women with CD4 Counts >250 cells/mm^3 or in ARV-Naive Men with CD4 Counts >400 cells/mm^3

Initiating NVP in ART-naive individuals with CD4 counts above these thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.[24-26] ART-experienced patients can safely switch to NVP if they have CD4 counts above these thresholds as a result of receiving effective ART **(BI)**.[27]

Unboosted Darunavir, Saquinavir, or Tipranavir

The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV, or in the case of DRV, also with COBI **(AII)**.

Stavudine plus Zidovudine

These NRTIs are antagonistic *in vitro*[28] and *in vivo*[29] **(AII)**.

Tenofovir Alafenamide plus Tenofovir Disoproxil Fumarate

This combination may be prescribed inadvertently, especially during transition from one formulation to another. There is no data supporting any potential additive efficacy or toxicity if TAF and TDF are used in combination.

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Management of the Treatment-Experienced Patient

Virologic Failure (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- Assessing and managing a patient who is experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
- Evaluation of virologic failure should include an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance test results.
- Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen **(AI)** or within 4 weeks of treatment discontinuation **(AII)**. Even if more than 4 weeks have elapsed since ARV drugs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII)**.
- The goal of treatment for ART-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays) **(AI)**.
- A new regimen should include at least two, and preferably three, fully active agents **(AI)**. A fully active agent is one that is expected to have uncompromised activity based on the patient's ART history and current and past drug-resistance test results. A fully active agent may also have a novel mechanism of action.
- In general, adding a single ARV agent to a virologically failing regimen **is not recommended**, because this may risk the development of resistance to all drugs in the regimen **(BII)**.
- For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued **(AI)** with regimens that are designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.
- It is crucial to provide continuous adherence support to all patients before and after regimen changes due to virologic failure.
- Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects (NTDs) in infants born to individuals who were receiving dolutegravir (DTG) at the time of conception; however, the risk of these defects is still low. In patients with virologic failure who are of childbearing potential and who are not using effective contraception or who are contemplating pregnancy, the following factors should be considered:
  - Clinicians should review Table 6b for information to consider when choosing to initiate or continue an integrase strand transfer inhibitor.
  - If there is an active ARV agent that can be used in place of DTG, DTG should not be prescribed **(AII)**.
  - If no alternatives exist, providers and patients should discuss the possible risk of NTDs and weigh that risk against the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after carefully considering these risks.
- When it is not possible to construct a viable suppressive regimen for a patient with multidrug-resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.
- When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 count, and an increase in the risk of clinical progression. Therefore, this strategy **is not recommended** in the setting of virologic failure **(AI)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral (ARV) regimens that are currently recommended for initial therapy in patients with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels that are below the lower limits of

detection (LLOD) of currently used assays (see What to Start). Patients on antiretroviral therapy (ART) who do not achieve this treatment goal or who experience virologic rebound can develop resistance mutations to one or more components of their regimen. Adherence to ART regimens can be challenging for some patients, and poor adherence can result in detectable viral loads. Depending on their treatment histories, some of these patients may have minimal or no drug resistance and others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients on ART and discusses strategies to manage ART in these individuals.

Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to ART:

Virologic Suppression: A confirmed HIV RNA level below the LLOD of available assays.

Virologic Failure: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

Incomplete Virologic Response: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen. A patient's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels.

Virologic Rebound: Confirmed HIV RNA level ≥200 copies/mL after virologic suppression.

Virologic Blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Low-Level Viremia: Confirmed detectable HIV RNA level <200 copies/mL.

Antiretroviral Therapy Treatment Goals and Presence of Viremia While on Antiretroviral Therapy

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels that are persistently suppressed below the LLOD of current assays.[1]

Virologic blips are not usually associated with subsequent virologic failure.[2] In contrast, there is controversy regarding the clinical implications of persistently low HIV RNA levels that are between the LLOD and <200 copies/mL in patients on ART. Viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than the PCR-based viral load platforms used in the past.[3-5] Findings from a large retrospective analysis showed that, as a threshold for virologic failure, HIV RNA levels of <200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound as HIV RNA levels of >200 copies/mL.[6] Two other retrospective studies also support the supposition that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.[7,8] However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound[9,10] and can be associated with the evolution of drug resistance.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common when HIV RNA levels are >500 copies/mL.[13] Therefore, patients who have persistent plasma HIV RNA levels ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.[14,15] The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.[16] Virologic failure may be associated with a variety of factors, including:

Patient/Adherence-Related Factors (see Adherence to the Continuum of Care)

- Comorbidities that may affect adherence (e.g., active substance abuse, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARV drugs (i.e., these factors may affect the ability to access or continue therapy)
- Adverse drug effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance test results
- Prior treatment failure
- Innate resistance to ARV drugs
- Higher pretreatment HIV RNA level (some regimens may be less effective at higher levels)

Antiretroviral Regimen-Related Factors

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or penetration into reservoirs)
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy, or the sequential introduction of drugs)
- Food requirements
- Adverse drug-drug interactions with concomitant medications
- Prescription errors

Managing Patients with Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above factors could have been the cause(s) of failure is indicated. Often the causes of virologic failure can be identified, but in some cases, they are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ depending on the cause. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be taken to improve virologic outcomes. Those approaches are outlined below.

Key Factors to Consider When Designing a New Antiretroviral Regimen

- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs, which should be selected after considering the patient's ART history and current and previous resistance test

results and whether an ARV drug with a new mechanistic action is available **(AI)**.[9,17-26]

- Despite the presence of some drug-resistance mutations, some ARV drugs in the regimen may still have partial activity against the patient's HIV and may be retained as part of a salvage regimen. These drugs may include NRTIs or protease inhibitors (PIs).[27] Other agents will likely have to be discontinued, as their continued use may lead to further accumulation of resistance mutations and jeopardize treatment options with newer drugs from the same drug class. These drugs may include enfuvirtide (T-20); non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz, nevirapine, and rilpivirine; and the first-generation integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and elvitegravir (EVG).[28-30]
- Using a drug that a patient has never used previously does not ensure that the drug will be fully active; there is a potential for cross-resistance among drugs from the same class.
- Archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question.
- When constructing a salvage regimen, it is more important to consider drug potency and viral susceptibility based on cumulative genotype data than the number of component drugs.
- Resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient's plasma HIV RNA level is >1,000 copies/mL **(AI)**, and possibly even if it is between 500 copies/mL and 1,000 copies/mL **(BII)** (see Drug-Resistance Testing). In some patients, resistance testing should still be considered even after treatment interruptions of >4 weeks, though clinicians should recognize that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels **(CIII)**. Drug resistance is cumulative; thus, clinicians should evaluate the extent of drug resistance, taking into account a patient's ART history and, importantly, prior genotypic or phenotypic resistance test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs; INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in patients who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for patients who experience failure on a fusion inhibitor **(AII)** and viral tropism tests for patients who experience failure on a CCR5 antagonist **(BIII)** are also available (see Drug-Resistance Testing).
- Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia **is not recommended**, as it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count, and it increases the risk of clinical progression **(AI)**[27,31] (see Discontinuation or Interruption of Antiretroviral Therapy).
- When changing an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see Hepatitis B (HBV)/HIV Coinfection).

The Use of Integrase Strand Transfer Inhibitors in Persons of Childbearing Potential

Because the use of INSTIs is frequently considered for persons who are experiencing virologic failure, clinicians should be aware that preliminary data from Botswana suggest that there is an increased risk of neural tube defects (NTDs) in infants born to individuals who were receiving dolutegravir (DTG) at the time of conception (0.9%).[32,33] Follow-up data showed that the prevalence of NTDs in infants who were exposed to DTG is lower than reported in the preliminary data (0.3%), but still higher than in infants born to women who received ART that did not include DTG (0.1%).[34,35] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review the information in Table 6b.

When DTG is the only treatment option (or one of few treatment options) for persons of childbearing potential with virologic failure, providers and patients should discuss the possible risk of NTDs and weigh

that risk against the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after carefully considering these risks.

Clinicians should note that there are insufficient safety data on the use of bictegravir (BIC) around the time of conception and during pregnancy to guide evidence-based recommendations. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.

Antiretroviral Drug Strategies

- In general, patients who receive at least three active drugs experience better and more sustained virologic response than those who receive fewer active drugs. These three drugs should be selected based on the patient's ART history and a review of their drug-resistance test results, both past and present.[18,19,21,22,36-38]
- Active drugs are ARV drugs that, based on current and previous resistance test results and ART history, are expected to have antiviral activity equivalent to the activity seen when there is no resistance to the specific drugs. ARV drugs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance.
- Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine, darunavir [DRV], and DTG).
- An active drug may also be one with a mechanism of action that is different from the mechanisms of the ARV drugs that were previously used in that individual (e.g., the fusion inhibitor T-20, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus, and some investigational ARV drugs).
- An increasing number of studies in ART-naive and ART-experienced patients have shown that an active, PK-enhanced PI plus one other active drug or several partially active drugs will effectively reduce viral load in most patients.[39-42]
- In the presence of certain resistance mutations, some ARV drugs, such as DTG, darunavir/ritonavir (DRV/r), and lopinavir/ritonavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus.[43,44]

Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous group of individuals with different ART exposure histories, degrees of drug resistance, durations of virologic failure, and levels of plasma viremia. Management strategies should be individualized. The first steps for all patients with detectable viral loads are to confirm the level of HIV viremia and assess and address adherence and potential drug-drug interactions (including interactions with over-the-counter products and supplements) and drug-food interactions. Some general approaches based on level of viremia are addressed below.

- **HIV RNA Above the LLOD and <200 copies/mL:** Patients who have these HIV RNA levels do not typically require a change in treatment **(AII)**.[4] Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future **(AIII)**.

- **HIV RNA Levels ≥200 copies/mL and <1,000 copies/mL:** In contrast to patients with detectable HIV RNA levels that are persistently <200 copies/mL, those with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[7,8] Patients who have persistent plasma HIV RNA levels in the range of 200 copies/mL to 1,000 copies/mL are considered to be experiencing virologic failure, and resistance testing should be attempted, particularly in patients with HIV RNA levels >500 copies/mL. Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL (as outlined below). When resistance testing cannot be performed because of low HIV

RNA levels, the decision of whether to empirically change ARV drugs should be made on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress viremia can be constructed.

- **HIV RNA ≥1,000 copies/mL and No Drug Resistance Mutations Identified Using Current or Previous Genotypic Resistance Test Results:** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment to determine the level of adherence, identify and address the underlying cause(s) for incomplete adherence and, if possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency; see Adherence to the Continuum of Care). Approaches include:
  - Assessing the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence.
  - Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV agent in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI; see Adverse Effects of Antiretroviral Agents).
  - Reviewing food requirements for each medication and assessing whether the patient adheres to the requirements.
  - Assessing whether there is a recent history of gastrointestinal symptoms (e.g., vomiting, diarrhea) that may result in short-term malabsorption.
  - Reviewing concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug-Drug Interactions and Tables 21a through 22b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
  - Considering therapeutic drug monitoring if PK drug-drug interactions or impaired drug absorption leading to decreased ARV drug exposure is suspected.
  - Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for >4 weeks before testing?).
    - If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen.
    - If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective but more tolerable regimen.
    - Repeat viral load testing 2 to 4 weeks after treatment is resumed or started; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged **(CIII)**.
- **HIV RNA >1,000 copies/mL and Drug Resistance Identified:** If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible in order to avoid progressive accumulation of resistance mutations.[45] In addition, several studies have shown that virologic responses to new and active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 counts at the time of regimen changes; thus, the change is best done before viremia worsens or CD4 count declines.[9,46] The availability of newer ARV drugs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most of these patients. The options in this setting depend on the extent of drug resistance and are addressed in the clinical scenarios outlined below.

Managing Virologic Failure in Different Clinical Scenarios

See Table 11 for a summary of these recommendations.

Virologic Failure with First Antiretroviral Regimen

- **NNRTI plus NRTI Regimen Failure:** These patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC). Additional NRTI mutations may also be present. Below are some switch options.
  - **Boosted PI plus Two NRTIs:** Three large randomized controlled trials (primarily conducted in resource-limited settings where NNRTI-based regimens have been used as first-line therapy) have explored different second-line regimen options. The studies found that regimens that contained LPV/r plus two NRTIs were as effective as regimens that contained LPV/r plus RAL.[41,42,47] Even though LPV/r was the PI used in these studies, it is likely that other boosted PIs (i.e., DRV/r or atazanavir/ritonavir) would have similar activities and may be tolerated better, although this has not been demonstrated in large clinical trials. The EARNEST study randomized participants to receive LPV/r plus two or three investigator-selected NRTIs, LPV/r plus RAL, or LPV alone. Participants did not undergo resistance testing before randomization.[42] Lower rates of virologic suppression were seen in participants who received LPV/r monotherapy, confirming that ritonavir-boosted PI (PI/r) monotherapy **cannot be recommended (AI)**.[42,48] The virologic responses were similar in the LPV/r plus NRTIs arm and the LPV/r plus RAL arm. A post-hoc analysis showed that viral suppression was achieved in over 80% of the participants who received either no active NRTIs or one active NRTI in their new regimens.[49] It should be noted that most of the participants received thymidine analogs (stavudine or zidovudine—NRTIs that are no longer used in first-line regimens in the United States) plus 3TC. The authors of this trial suggest that, as a public health approach, resistance testing after first-line failure may not be necessary in resource-limited countries. However, in settings where genotypic resistance tests are available, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends using a boosted PI plus two NRTIs (at least one of which is active) in a regimen **(AIII)**.
  - **DTG plus One or Two Active NRTIs:** In the DAWNING trial, patients who experienced virologic failure while on a first-line, NNRTI-based regimen were randomized to receive either LPV/r or DTG; each of these drugs was given with two NRTIs, one of which had to be fully active based on real-time resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm.[50] Thus, DTG plus two NRTIs (at least one of which is active) can be an option after failure of a first-line, NNRTI-based therapy **(AI)**. BIC may have activity that is similar to that of DTG; however, there are currently no data to support its use. There are not enough data on the efficacy of EVG or RAL to recommend the use of these INSTIs in the setting of first-line, NNRTI-based therapy failure.
  - **Boosted PI plus an INSTI:** As noted earlier, a regimen that consisted of LPV/r plus RAL was found to be as effective as LPV/r plus two NRTIs.[41,42,47] Thus, LPV/r plus RAL can also be a treatment option for those who experienced virologic failure on an NNRTI-based regimen **(AI)**. Although data are limited, DTG combined with a boosted PI may also be an option in this setting **(AIII)**. There are no data on the efficacy of BIC or EVG with boosted PI in the setting of first-line, NNRTI-based therapy failure.
- **Boosted PI plus NRTI Regimen Failure:** In this scenario, most patients will have either no resistance or resistance that is limited to 3TC and FTC.[51,52] Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. Below are some management options.
  - **Maintain on the Same Regimen:** A systematic review of multiple randomized trials that investigated the failures of first-line, PI/r-based regimens showed that maintaining the same regimen while making efforts to enhance adherence is as effective as changing to new regimens with or without drugs from new classes **(AII)**.[53] If the regimen is well tolerated and there are no concerns about drug-drug or drug-food interactions or drug resistance, then the regimen can be continued with

adherence support and viral monitoring.

- **Switch to Another Regimen:** If poor tolerability, drug interactions, or drug resistance may be contributing to virologic failure, then the regimen can be modified to:
  - A different boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
  - A different boosted PI plus an INSTI **(BIII)**; *or*
  - An INSTI plus two NRTIs (at least one of which is active) **(AIII)**. As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is the recommended INSTI **(AIII)**. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. There are limited to no data on the efficacy of BIC or EVG in this setting.

- **INSTI plus NRTI Regimen Failure:** Virologic failure in patients on a regimen that consists of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC or FTC and possibly the INSTI.[54] Viruses with EVG or RAL resistance often remain susceptible to DTG.[46] In contrast, in clinical trials, persons who experienced virologic failure while receiving BIC or DTG plus two NRTIs as first-line therapy were unlikely to develop phenotypic resistance to BIC or DTG.[54-56] There are no clinical trial data to guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on resistance test results and the potential potency of the next regimen. Below are some treatment options, based on resistance pattern considerations.
  - **Virologic Failure without Any Resistance Mutations:** The patient should be managed as outlined above in the section on virologic failure without resistance.
  - **Virologic Failure without INSTI Resistance:** The regimen can be modified to
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - A boosted PI plus an INSTI **(AIII)**; *or*
    - DTG plus two NRTIs (at least one of which is active) **(AIII)**.
  - **Virologic Failure with Resistance to RAL and EVG but Susceptibility to DTG:** The regimen can be modified to:
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus a boosted PI **(AIII)**.

There are currently no data on the efficacy of BIC in patients who experience virologic failure while on an EVG- or RAL-based regimen; therefore, this drug cannot be recommended in this setting.

Second-Line Regimen Failure and Beyond

Drug Resistance with Fully Active Antiretroviral Therapy Options

Using a patient's treatment history and drug-resistance data, a clinician can decide whether to include a fully active, boosted PI in future regimens. For example, those who have no documented PI resistance and who have previously never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. In this setting, viral suppression should be achievable using a boosted PI combined with either two NRTIs or an INSTI—provided the virus is susceptible to these drugs. If a fully active, boosted PI is not an option, the new regimen should include at least two, and preferably three, fully active agents. Drugs should be selected based on the likelihood that they will be active, as determined by the patient's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug Resistance without Fully Active Antiretroviral Therapy Options

Use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug resistance.[57,58] Despite this progress, there remain patients who have experienced toxicities with and/or developed resistance to all or most currently available drugs. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens.

Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T-20, DTG, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, as there is little evidence that keeping them in the regimen helps delay disease progression **(BII)**. Moreover, continuing these drugs (in particular INSTIs) may allow for selection of additional resistance mutations and development of within-class cross resistance that may limit future treatment options. It should be noted that even partial virologic suppression of HIV RNA to >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit.[57,59] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 count increases, reduces the risk of disease progression.[60] Other cohort studies suggest that even modest reductions in HIV RNA levels continue to confer immunologic and clinical benefits.[61,62] However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single fully active ARV drug to the regimen **is not recommended** because of the risk of rapid development of resistance **(BII)**.

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for the recently approved CD4 post-attachment inhibitor ibalizumab (IBA).[63] A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV and who were experiencing virologic failure on an ARV regimen. Subjects received intravenous infusions of IBA every 2 weeks in addition to an optimized background regimen that included at least one additional agent to which the subject's virus was susceptible. At Week 24, 43% of participants achieved HIV RNA <50 copies/mL, and 50% of participants achieved HIV RNA <200 copies/mL.[64] Of the 27 participants who continued on to the 48-week follow-up study, 59% and 63% had HIV RNA <50 copies/mL and <200 copies/mL, respectively. All 15 patients who had HIV RNA <50 copies/mL at Week 24 maintained viral suppression up to Week 48.[65]

Patients who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in Food and Drug Administration regulations. Information about agents that are in late-stage clinical studies (e.g., fostemsavir, PRO-140), can be found in the drug fact sheets available on AIDS*info*'s website.

Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Resistance Test Results)

Every effort should be made to obtain the patient's ARV history and prior drug-resistance test results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be active based on the patient's treatment history. If no ARV history is available, a clinician may consider using agents with a high barrier to resistance, such as twice-daily DTG and/or boosted DRV, as part of the regimen. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. HIV RNA and resistance testing should be obtained approximately 2 to 4 weeks after re-initiation of therapy, and patients should be closely monitored for virologic responses. Lastly, since there are no safety data on the use of BIC around the time of conception to guide evidence-based recommendations, an approach similar to that outlined for DTG may be implemented before considering the use of BIC-containing ART in those of childbearing potential.

Table 11. Antiretroviral Options for Patients with Virologic Failure

Designing a new regimen for patients who are experiencing treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. For more detailed descriptions, please refer to the text above and/or consult an expert in drug resistance to assist in the design of a new regimen. It is also crucial to provide continuous adherence support to all patients before and after regimen changes.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- 3TC or FTC (i.e., NNRTI mutations +/- M184V/I).[c] Additional NRTI mutations may also be present.	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d] plus two NRTIs (at least one active) **(AI)**; *or* Boosted PI plus INSTI **(AIII)**	Resuppression
	Boosted PI plus two NRTIs	Most likely no resistance, or resistance only to 3TC or FTC (i.e., M184V/I, without resistance to other NRTIs)[c]	Continue same regimen **(AII)**; *or* Another boosted PI plus two NRTIs (at least one active) **(AII)**; *or* INSTI plus two NRTIs (at least one active; if only one of the NRTIs is fully active, or if adherence is a concern, DTG[d] is preferred over other INSTIs) **(AIII)**; *or* Another boosted PI plus INSTI **(BIII)**	Resuppression
	INSTI plus two NRTIs	No INSTI resistance (can have 3TC or FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs)[c]	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d] plus two NRTIs (at least one active) **(AIII)**; *or* Boosted PI plus INSTI **(BIII)**	Resuppression
		EVG or RAL +/- 3TC or FTC resistance Resistance to first-line BIC or DTG is rare.	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d,e] twice daily (if HIV is sensitive to DTG) plus two active NRTIs **(AIII)**; *or* DTG[d,e] twice daily (if HIV is sensitive to DTG) plus a boosted PI **(AIII)** BIC has not been studied in this setting and **cannot be recommended**.	Resuppression
Second Regimen Failure and Beyond	Drug resistance with active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen.	At least two, and preferably three, fully active agents **(AI)** Partially active drugs may be used when no other options are available. Consider using an ARV drug with a different mechanism of action.	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure, continued

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
Second Regimen Failure and Beyond, continued	Multiple or extensive drug resistance with few treatment options	Use past and current genotypic and phenotypic resistance testing to guide therapy. Consider viral tropism assay when use of MVC is considered. Consult an expert in drug resistance, if needed.	Identify as many active or partially active drugs as possible based on resistance test results. Consider using an ARV drug with a different mechanism of action. Consider enrollment into clinical trials or expanded access programs for investigational agents, if available. Discontinuation of ARV drugs **is not recommended**.	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 count as high as possible.
ART-Experienced Patients with Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History	Unknown	Obtain medical records, if possible. Resistance testing may be helpful in identifying drug resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	Consider restarting the old regimen, and obtain viral load and resistance testing 2–4 weeks after reintroduction of therapy. If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG[d,e] and/or boosted DRV).	Resuppression

[a] There are insufficient data to provide a recommendation for the continuation of 3TC or FTC in the presence of M184V/I.

[b] When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[c] If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

[d] Data from an observational study in Botswana suggest that there is an increased risk of NTDs in infants born to individuals who were receiving DTG at the time of conception; however, the risk of these defects is still low. Please refer to the discussion in the text and in Table 6b before prescribing DTG in persons of childbearing potential.

[e] Response to DTG depends on the type and number of INSTI mutations.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of "compartmentalized" virologic failure. These patients present with new, usually subacute, neurological symptoms that are associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.[66-68] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.[69] Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, there is evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen according to the principles outlined above for plasma HIV RNA resistance **(CIII)**. In these patients, it may also be useful to consider CNS PKs during drug selection to assure adequate concentrations of drugs within the CNS **(CIII)**. If CSF HIV resistance testing is not available, the regimen may be changed based on the patient's treatment history or on predicted drug penetration into the CNS **(CIII)**.[70-73]

This "neurosymptomatic" CNS viral escape should be distinguished from:

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation, which is similar to plasma blips in that it is usually transient with low levels of CSF HIV RNA;[74,75] *or*
- A transient increase in CSF HIV RNA that is related to other CNS infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster).[76]

There does not appear to be an association between these asymptomatic CSF HIV RNA elevations and the relatively common chronic, usually mild, neurocognitive impairment in patients with HIV who show no evidence of CNS viral breakthrough.[77] Unlike the "neurosymptomatic" CNS viral escape, these latter conditions do not currently warrant a change in ART.[78]

Summary

The management of ART-experienced patients with virologic failure often requires expert advice to construct virologically suppressive regimens. Before modifying a regimen, it is critical to carefully evaluate the potential cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug-drug and drug-food interactions, as well as review HIV RNA and CD4 count changes over time, complete treatment history, and current and previous drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider the use of investigational agents through participation in clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 counts to delay clinical progression.

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Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel's Recommendations

- Morbidity and mortality from several AIDS and non-AIDS conditions are increased in individuals with HIV despite antiretroviral therapy (ART)-mediated viral suppression, and are predicted by persistently low CD4 T lymphocyte (CD4) cell counts and/or persistent immune activation.
- ART intensification by adding antiretroviral (ARV) drugs to a suppressive ART regimen does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(AI)**.
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(BIII)**.
- No interventions designed to increase CD4 cell counts and/or decrease immune activation are recommended at this time (in particular, interleukin-2 **is not recommended [AI]**) because no intervention has been proven to decrease morbidity or mortality during ART-mediated viral suppression.
- Monitoring markers of immune activation and inflammation **is not recommended** because no immunologically targeted intervention has proven to improve the health of individuals with abnormally high biomarker levels, and many markers that predict morbidity and mortality fluctuate widely in individuals **(AII)**.
- Because there are no proven interventions to improve CD4 cell recovery and/or inflammation, efforts should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and exercise; treating hypertension and hyperlipidemia) **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in individuals with HIV continues to be greater than in the general population, particularly when ART is delayed until advanced disease stages. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type II diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and frailty.[1] Although health-related behaviors and toxicities of antiretroviral (ARV) drugs may also contribute to the increased risk of illness and death, poor CD4 T lymphocyte (CD4) cell recovery, persistent immune activation, and inflammation likely also contribute to the risk.

Poor CD4 Cell Recovery

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most individuals with HIV will continue to increase for at least a decade. The rate of CD4 cell recovery is typically most rapid in the first 3 months of suppressive ART, followed by more gradual increases over time.[2-4] If ART-mediated viral suppression is maintained, most individuals will eventually recover CD4 counts in the normal range (>500 cells/mm^3); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm^3) may plateau at abnormally low CD4 cell counts.[3-5] Early initiation of ART in individuals with recent HIV diagnoses likely provides the best opportunity for maximal CD4 cell recovery.[6]

Persistently low CD4 cell counts despite ART-mediated viral suppression are associated with increased risk of morbidity and mortality. For example, individuals with HIV who have CD4 counts <200 cells/mm^3 despite at least 3 years of suppressive ART had a 2.6-fold greater risk of mortality than those with higher CD4 cell counts.[7] Lower CD4 cell counts during ART-mediated viral suppression are associated with an increased risk of non-AIDS morbidity and mortality,[8-11] including cardiovascular disease,[12] osteoporosis and

fractures,[13] liver disease,[14] and infection-related cancers.[15] The prognostic importance of higher CD4 cell counts likely spans all ranges of CD4 cell counts, though incremental benefits are harder to discern once CD4 counts increase to >500 cells/mm^3.[16]

Individuals with poor CD4 cell recovery should be evaluated for modifiable causes of CD4 cell lymphopenia. Concomitant medications should be reviewed, with a focus on those known to decrease white blood cells or, specifically, CD4 cells (e.g., cancer chemotherapy, interferon, zidovudine,[17] or the combination of tenofovir disoproxil fumarate [TDF] and didanosine [ddI]).[18,19] If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., HCV, HIV-2) and serious medical conditions (e.g., malignancy) should also be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and/or in those with CD4 counts consistently below 100 cells/mm^3. In many cases, no obvious cause for suboptimal immunologic response can be identified.

Despite strong evidence linking low CD4 cell counts and increased morbidity during ART-mediated viral suppression, no adjunctive therapies that increase CD4 cell count beyond levels achievable with ART alone have been proven to decrease morbidity or mortality. Adding ARV drugs to an already suppressive ART regimen does not improve CD4 cell recovery,[20-25] and does not reduce morbidity or mortality. Therefore, ART intensification is not recommended as a strategy to improve CD4 cell recovery **(AI)**. In individuals maintaining viral suppression, switching ARV drug classes in a suppressive regimen also does not consistently improve CD4 cell recovery and is not recommended **(BIII)**.[26] Two large clinical trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2, an immune-based therapy, in improving CD4 cell recovery. Interleukin-2 adjunctive therapy resulted in CD4 cell count increases but with no observable clinical benefit. Therefore, interleukin-2 **is not recommended (AI)**.[27] Other immune-based therapies that increase CD4 cell counts (e.g., growth hormone, interleukin-7) are under investigation. However, none of the therapies have been evaluated in clinical endpoint trials; therefore, whether any of these approaches will offer clinical benefit is unclear. Currently, such immune-based therapies should not be used except in the context of a clinical trial.

Persistent Immune Activation and Inflammation

Although poor CD4 cell recovery likely contributes to morbidity and mortality during ART-mediated viral suppression, there is increasing focus on persistent immune activation and inflammation as potentially independent mediators of risk. HIV infection results in heightened systemic immune activation and inflammation, effects that are evident during acute infection, persist throughout chronic untreated infection, and predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels.[28] Although immune activation declines with suppressive ART, it often persists at abnormal levels in many individuals with HIV maintaining long-term ART-mediated viral suppression—even in those with CD4 cell recovery to normal levels.[29,30] Immune activation and inflammatory markers (e.g., IL-6, D-dimer, hs-CRP) also predict mortality and non-AIDS morbidity during ART-mediated viral suppression, including cardiovascular and thromboembolic events, cancer, neurocognitive dysfunction, and frailty.[28] Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm^3) tend to have greater immune activation and inflammation than those with greater recovery,[29] the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count.[31,32] Even in individuals with CD4 counts >500 cells/mm^3, there is evidence that immune activation and inflammation contribute to morbidity and mortality.[33] Thus, innate immune activation and inflammation are potentially important targets for future interventions.

Although the drivers of persistent immune activation during ART are not completely understood, HIV persistence, coinfections, and microbial translocation likely play important roles.[28] Interventions to reduce each of these presumed drivers are currently being investigated. Importantly, adding ARV drugs to an already suppressive ART regimen (ART intensification) does not consistently improve immune activation.[20-23,25]

Although some studies have suggested that switching an ART regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,[34,35] these studies have limitations and results are not consistent across markers and among studies. Thus, at this time, ART modification cannot be recommended as a strategy to reduce immune activation **(BIII)**. Other commonly used medications with anti-inflammatory properties (e.g., statins, aspirin) are being studied, and preliminary evidence suggests that some may reduce immune activation in treated HIV infection.[36,37] However, because no intervention specifically targeting immune activation or inflammation has been studied in a clinical outcomes trial in treated HIV infection, no interventions to reduce immune activation are recommended at this time.

In the absence of proven interventions, there is currently no clear rationale to monitor levels of immune activation and inflammation in treated HIV infection. Furthermore, many of the inflammatory markers that predict morbidity and mortality fluctuate significantly in individuals with HIV. Thus, clinical monitoring with immune activation or inflammatory markers **is not currently recommended (AII)**. The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities such as hypertension, hyperlipidemia, and diabetes **(AII)**.

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Optimizing Antiretroviral Therapy in the Setting of Viral Suppression (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Panel's Recommendations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching a person with HIV from an effective regimen to an alternative regimen in some situations.
• The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options.
• Adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch.
• It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results, before selecting a new antiretroviral therapy regimen **(AI)**.
• Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switch strategy **is not recommended (AI)**.
• When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV infection should be continued **(AII)**. Using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII)**, as HBV resistance to these drugs can emerge. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.
• Consultation with an HIV specialist is recommended when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.
• Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

With currently available antiretroviral therapy (ART), most persons with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in antiretroviral (ARV) treatment and a better understanding of drug resistance make it possible to consider switching a person with HIV from one effective regimen to another in some situations (see below). When considering such a switch, clinicians must keep several key principles in mind to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 18 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see the Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Optimization

Maintain Viral Suppression

The fundamental principle of regimen optimization is to maintain viral suppression without jeopardizing future treatment options. If a regimen switch results in virologic failure with the emergence of new resistance

mutations, the patient may require more complex and/or expensive regimens.

Careful Review of Antiretroviral Treatment and Drug Resistance History Before Optimization

The review of a patient's full ARV history—including virologic responses and past ARV-associated intolerances, toxicities, and adverse reactions—is critical before any treatment switch **(AI)**.

If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can safely assume that no new drug resistance mutation emerged while the patient was on the suppressive regimen. In patients with a history of virologic failure or pre-treatment drug resistance, review of cumulative resistance test results and clinical response to prior regimens is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a drug-resistance mutation—even when it is not detected in the patient's most recent drug resistance test—can be archived in the HIV reservoir and is likely to re-emerge under the appropriate selective drug pressure. When resistance data are not available, resistance can often be inferred from a patient's ARV history. For patients with documented failure on a regimen that includes drugs with relatively low barriers to resistance, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), elvitegravir (EVG), raltegravir (RAL), lamivudine (3TC), or emtricitabine (FTC), one should assume that there is resistance to these drugs. If there is uncertainty about prior resistance, it is generally not advisable to switch a suppressive ARV regimen unless the new regimen is likely to be at least as active against potential resistant virus as the current suppressive regimen. This principle is particularly applicable when switching ARV-experienced individuals from a regimen with a relatively high barrier to resistance, such as those that include pharmacologically boosted protease inhibitors (PIs), dolutegravir (DTG), or bictegravir (BIC), to one with a lower barrier to resistance.[1] The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends that clinicians consult an HIV specialist when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes **(AIII)**.

If regimen switching is considered in patients with suppressed viral loads who do not have prior drug resistance data, proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or for those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide valuable information. In individuals with a history of multiple prior failures or multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, whenever proviral DNA genotypic testing is used, the results must be interpreted with caution because these assays may not detect all of a patient's drug resistance mutations, especially those that were selected by a previous ART regimen. In addition, these assays may identify mutations that appear to be inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

Optimization in a Person with Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless these drugs are contraindicated. Both TDF and TAF are active against HBV.[2] Discontinuation of these drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage. In persons with HIV/HBV coinfection, using 3TC or FTC as the only drug in a regimen with HBV activity **is not recommended (AII)**, as HBV resistance to these drugs can emerge. If TDF or TAF cannot be used as part of the ARV regimen, refer to Hepatitis B Virus/HIV Coinfection for recommendations.

Assess for Potential Drug Interactions

Before switching a regimen, it is important to review the ARV drugs in the new regimen and concomitant

medications to assess whether there are any potential drug-drug interactions. For example, rilpivirine (RPV) may interact with acid-lowering agents, and TAF and BIC may interact with rifamycins (see Drug-Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs may also necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic (PK) boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications which may have previously been managed with dose adjustments will need to be re-evaluated in the context of the new ART regimen.

Assess for Potential for Pregnancy and Use of INSTI in Persons of Childbearing Potential

Persons of childbearing potential should have a pregnancy test before switching ART. If a person with HIV is found to be pregnant, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use in pregnancy.

Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen. Preliminary data from a study conducted in Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[3,4] Follow-up data, however, showed that the prevalence of infant NTDs in association with maternal DTG exposure at conception is lower (0.3%), but still higher than in infants exposed to non-DTG containing ARV regimens (0.1%).[5,6] There are insufficient safety data on the use of BIC around the time of conception and during pregnancy to determine whether it is safe. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.

Monitoring after Switch

Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (see below).

Specific Regimen Optimization Considerations

As with ART-naive patients, the use of a two-drug (as discussed below) or three-drug combination regimen is generally recommended when switching patients with suppressed viral loads **(AI)**. Patients who have no resistance mutations or history of virologic failure can likely switch to any regimen that has been shown to be highly effective in ART-naive patients. Patients with prior drug resistance can be switched to a new regimen based on their ARV history and resistance testing results. Monotherapy with either a boosted PI or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than combination regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, **monotherapy as an optimization strategy is not recommended (AI)**.

Optimization Strategies with Good Supporting Evidence for Persons with No History of Drug Resistance

Many clinical trials have enrolled participants with stably suppressed viral loads without underlying drug resistance and switched them to another regimen, typically including at least two fully active drugs. Most of these studies demonstrated maintenance of viral suppression; some of these studies are referenced below. The SWITCHMRK 1 and 2 studies illustrated the importance of considering the possibility of underlying drug resistance before switching therapy in those with virologic suppression.[1] This is particularly important when the new regimen may not include three fully active agents. In the two SWITCHMRK studies, those with viral suppression on two NRTIs plus lopinavir/ritonavir (LPV/r) were switched to two NRTIs plus RAL. The studies showed that individuals with a history of previous virologic failure had an increased risk of virologic failure when switching to the RAL-based regimen. A possible explanation for this finding is that,

when only one of the accompanying NRTIs is fully active, viral suppression can be maintained by drugs with relatively high barriers to resistance, such as boosted PIs, DTG, and BIC, but not by those with lower barriers to resistance such as EVG, RAL, and NNRTIs. The strategies listed below support these observations and principles of optimizing therapy.

Three-Drug Regimens

Within-Class Switches

Within-class switches may be prompted by adverse events or the availability of ARVs in the same class that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, lower pill burden, or do not require PK boosting. Within-class switches usually maintain viral suppression, provided there is no drug resistance to the new ARV. Some examples of within-class switch strategies that have been studied in individuals without underlying drug resistance include switching from:

- TDF[7,8] or abacavir (ABC)[9] to TAF
- RAL to DTG
- DTG,[10,11] EVG/c,[12] or RAL to BIC
- Efavirenz (EFV) to RPV,[8,13] or to doravirine (DOR)[14]
- Boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with ABC/3TC)[15-17]

Between-Class Switches

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. In general, such switches should be avoided if there is any doubt about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch. The following are between-class switches that have been studied:

- Replacing a boosted PI with an INSTI (e.g., DTG,[18] BIC,[19] or EVG[20,21])
- Replacing a boosted PI with RPV[22] or DOR[14]
- Replacing an NNRTI with an INSTI[23,24]
- Replacing a boosted PI with maraviroc (MVC).[25] When switching to MVC, co-receptor usage in patients with virologic suppression can be determined from proviral DNA (see Co-receptor Tropism Assays).[25-27]

Two-Drug Regimens

There is growing evidence that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved virologic suppression with three-drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, since none of the two-drug regimens discussed below has adequate anti-HBV activity, these regimens are not recommended for individuals with HBV coinfection **(AIII)**. Below are examples of successful strategies for switching from three- to two-drug regimens in persons with suppressed HIV.

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for ≥1 year (defined by no HIV RNA >50 copies/mL in the past 6 months, and no more than one instance of HIV RNA 50–200 copies/mL in the 6–12 months before enrollment) who were on their first or second regimen and had no history of virologic failure and no documented evidence of any major drug-resistance mutations.[28] Participants were randomized to remain on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV (early-switch arm). Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. At 52 weeks, those who were randomized to remain on their current regimens were allowed to switch to DTG plus RPV (late-switch arm). At 100 weeks, 89% of participants in the early-switch arm and 93% of those in the late-switch arm maintained HIV RNA <50 copies/mL.[29] DTG plus RPV is available as a

coformulated single-tablet regimen. It is a reasonable option when the use of nucleoside reverse transcriptase inhibitors (NRTIs) is not desirable. DTG plus RPV should only be given to patients who do not have chronic HBV infection, have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce the concentration of either drug **(AI)**.

Dolutegravir plus Lamivudine

A switch from three-drug regimens to DTG plus 3TC as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO),[30] in two small clinical trials,[31,32] and in observational studies[33,34] with good success. The result of the TANGO trial is discussed below.

The Phase 3 TANGO study enrolled participants who were on their first ARV regimen with HIV RNA <50 copies/mL for ≥6 months. Participants were randomized to switch to open label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. At week 48, switching to DTG plus 3TC was non-inferior to continuing on the current regimen, with 93% of participants in both arms maintaining HIV RNA <50 copies/mL. No unexpected adverse events were identified as related to DTG or 3TC.[30] Switching to a DTG plus 3TC regimen can be a good option for individuals who have no evidence of resistance to either drug and do not have HBV coinfection **(AI)**.

Ritonavir-Boosted Protease Inhibitor plus Lamivudine

A ritonavir-boosted protease inhibitor (PI/r) plus 3TC may be a reasonable option when the continued use of TDF, TAF, or ABC is contraindicated or not desirable. There is growing evidence that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, who achieved sustained viral suppression for ≥1 year, and who have no evidence of, or risk for drug resistance to, either the PI/r or 3TC. Examples of boosted PI plus 3TC regimens that have been studied in clinical trials include the following:

- ATV/r plus 3TC **(CI)**,[35,36]
- Darunavir/ritonavir (DRV/r) plus 3TC **(BI)**,[37]
- LPV/r plus 3TC **(CI)**.[38]

Boosted Darunavir plus Dolutegravir

An open-label, Phase 3b, non-inferiority clinical trial randomized 263 participants who were on boosted DRV plus two NRTIs to continue on the same regimen or switch to boosted DRV plus DTG (study recruitment was stopped prematurely due to slow recruitment). At 48 weeks, the study demonstrated that switching to DTG plus boosted DRV was non-inferior to continuing triple therapy. In both arms, approximately 87% of participants maintained viral suppression at HIV RNA <50 copies/mL, and both groups had comparable rates of adverse events.[39] Because of the small sample size of this study, the regimen of boosted DRV plus dolutegravir is only recommended if there are no other alternative options **(CI)**. Similar results were observed in two small observational studies (13 participants and 56 participants).[40,41]

Optimization Strategies for Persons with Viral Suppression and a History of Limited Drug Resistance

There are some data demonstrating the safety and efficacy of within-class switches for individuals with underlying drug resistance who are on a stable ARV regimen with suppressed HIV RNA. However, there are limited data regarding between-class switches in this population, and support for such a switch generally depends on findings extrapolated from other studies, as discussed below.

Within-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from DTG to BIC [BI])

The GS 4030 study enrolled 565 individuals who were stably suppressed on DTG plus two NRTIs. The participants were randomized to either remain on their current regimen or switch to BIC/FTC/TAF. After 48

weeks, the groups had similar rates of sustained suppression.[42] The rates of viral suppression were similar for those with a documented history of NRTI resistance (approximately 25% of participants) and those without a history of NRTI resistance.[43]

Between-Class Switch from One High-Resistance Barrier Drug to Another (e.g., from a Boosted PI to a BIC- or DTG-Containing Regimen with At Least One Fully Active NRTI)

The GS 4030 study provides theoretical support for replacing a boosted PI-regimen with a BIC- or DTG-containing regimen, if at least one of the NRTIs in the regimen is fully active.[42,43] Although there are no switch studies testing this strategy, based on the GEMINI studies in treatment-naive patients, a DTG plus 3TC regimen (**when both ARVs are fully active**) is highly effective. In addition, the TANGO study (described above), demonstrated that in the setting of no underlying drug resistance, DTG plus 3TC, as the active NRTI, was a very effective switch strategy. In the DAWNING study,[44] in the setting of virologic failure with underlying NRTI resistance, DTG plus one fully active NRTI was more effective than LPV/r plus one fully active NRTI. Based upon standard optimization principles, if DTG plus two NRTIs, one of which is fully active, was effective in those with virologic failure, it should also be effective in those already virologically suppressed **(BIII)**.

Optimization Strategies for Persons with Viral Suppression and a History of Complex Underlying Resistance

Before optimization of the ARV regimen of a person with viral suppression who has a history of treatment failure and drug resistance, a careful review of the individual's ARV history and cumulative drug resistance profile should be undertaken. Consultation with a clinician with expertise in HIV drug resistance is recommended **(AIII)**.

One randomized controlled trial conducted in this patient population is described below.

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

Switching to the combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential optimization strategy in patients on complicated salvage regimens.[45] A randomized controlled trial enrolled 135 patients with virologic suppression who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Participants had up to three thymidine analog resistance mutations and/or the K65R mutation, but no history of either the Q151M mutation or T69 insertion. The participants were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their current regimen. At 48 weeks, optimization to EVG/c/TAF/FTC plus DRV was superior to continuation on a current regimen with 94.4% of participants in the switch arm and 76.1% in the continuation arm maintaining viral suppression. With regimen simplification, the pill burden was reduced from an average of five tablets per day to two tablets per day. EVG/c/TAF/FTC plus DRV would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study **(AI)**.

Optimization Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy

The strategy of switching patients with virologic suppression without PI resistance from one ART regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients, but at lower rates than regimens that include one or two NRTIs.[46-48] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs. In most studies, resuming NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.[49-52] No clinical trials have evaluated the use of coformulated PI/c regimens as monotherapy or compared different PI/r monotherapy regimens. Based on the results from these studies, boosted-PI monotherapy **is not recommended (AI)**.

Dolutegravir Monotherapy

The strategy of switching patients with virologic suppression to DTG monotherapy has been evaluated in cohort studies and in clinical practice[53,54] and in a randomized controlled trial.[55] This strategy has been associated with an unacceptable rate of virologic failure and subsequent development of INSTI resistance; therefore, a switch to DTG monotherapy **is not recommended (AI)**.

Boosted Atazanavir plus Raltegravir

In a randomized study, patients with virologic suppression switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the switch to ATV/r plus TDF/FTC.[56] A regimen consisting of ATV/r plus RAL **cannot currently be recommended (AI)**.

Maraviroc plus Boosted Protease Inhibitor

In a randomized controlled trial, patients with virologic suppression who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their current regimen or to switch to MVC plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuation than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC **cannot be recommended (AI)**.[57]

Maraviroc plus Raltegravir

In a nonrandomized pilot study, patients with virologic suppression were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in five out of 44 patients.[58] Based on these study results, use of MVC plus RAL **is not recommended (AII)**.

Monitoring after Treatment Changes

After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or phone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) **(AIII)**. The purpose of this close monitoring is to assess medication tolerance and to conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormality is a reason for the ARV change or is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

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Discontinuation or Interruption of Antiretroviral Therapy (Last updated April 8, 2015; last reviewed April 8, 2015)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression.[1-5] Thus, planned interruptions of ART are not generally recommended. However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or interrupted access to drugs. Stopping ART for a short time (i.e., less than 1 to 2 days) because of a medical/surgical procedure can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Short-Term Therapy Interruption

When a Patient Experiences a Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications:

- All components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short-Term Therapy Interruption (Up to 2 Weeks)

When All Regimen Components Have Similar Half-Lives and Do Not Require Food for Proper Absorption:

- All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.

When All Regimen Components Have Similar Half-Lives and Require Food for Adequate Absorption, and the Patient Cannot Take Anything by Mouth for a Short Time:

- Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

When the Antiretroviral Regimen Contains Drugs with Different Half-Lives:

- Stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]), which may increase the risk of selection of NNRTI-resistant mutations. Some experts recommend stopping the NNRTI first and the other antiretroviral drugs 2 to 4 weeks later. Alternatively, the NNRTI may be replaced with a ritonavir- or cobicistat-boosted protease inhibitor (PI/r or PI/c) for 4 weeks. The optimal time sequence for staggered discontinuation of regimen components, or replacement of the NNRTI with a PI/r or PI/c, has not been determined.

Planned Long-Term Therapy Interruptions

Planned long-term therapy interruptions are **not recommended** outside of controlled clinical trials **(AI)**. Several research studies are evaluating approaches to a functional (virological control in the absence of therapy) or sterilizing (virus eradication) cure of HIV infection. Currently, the only way to reliably test the effectiveness of these strategies may be to interrupt ART and closely monitor viral rebound over time in the setting of a clinical trial.

If therapy must be discontinued, patients should be aware of and understand the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for

chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

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Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early) HIV Infection (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV, including those with early[a] HIV infection **(AI)**. ART should be initiated as soon as possible after HIV diagnosis **(AII)**.
- The goal of ART is to suppress plasma HIV RNA to undetectable levels **(AI)** and to prevent transmission of HIV **(AI)**. Testing for plasma HIV RNA levels, CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as recommended for persons with chronic HIV infection **(AII)**.
- A sample for genotypic testing should be sent before initiation of ART **(AIII)**. ART can be initiated before drug resistance testing and HLA B*5701 test results are available. In this setting, one of the following ART regimens is recommended **(AIII)**:
  - Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - Dolutegravir (DTG) with (TAF or tenofovir disoproxil fumarate [TDF])[b] plus (FTC or lamivudine [3TC])
  - Boosted darunavir (DRV) with (TAF or TDF)[b] plus (FTC or 3TC)
- Pregnancy testing should be performed in individuals of childbearing potential before initiation of ART **(AIII)**.
- Data from an observational study in Botswana suggest there may be an increased risk of neural tube defects in infants born to individuals who were receiving DTG at the time of conception. Before initiating an integrase strand transfer inhibitor-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.
- As there are no safety data for BIC use around the time of conception, an approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.
- When the results of drug resistance and HLA-B*5701 testing are available, the treatment regimen can be modified if needed **(AII)**.
- Providers should inform individuals starting ART of the importance of adherence to achieve and maintain viral suppression **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

[a] Early infection represents either acute or recent infection.

[b] TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

Introduction

Acute HIV infection is the phase of HIV disease that occurs immediately after transmission, which is typically characterized by viremia as detected by the presence of HIV RNA or p24 antigen. Anti-HIV antibodies are not yet detectable early during this phase of HIV infection. Recent HIV infection is generally considered the phase of HIV disease ≤6 months after infection, during which anti-HIV antibodies develop and become detectable. Throughout this section, the term "early HIV infection" is used to refer to either acute or recent HIV infection. Persons with acute HIV infection may experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms; however, illness is generally nonspecific and can be relatively mild or the person can be asymptomatic.[1-6] Clinicians may fail to recognize acute HIV infection because its manifestations are often similar to those of many other viral infections, such as influenza and infectious mononucleosis. Table 12 provides practitioners with guidance to recognize, diagnose, and manage acute HIV infection.

Diagnosing Acute HIV Infection

Health care providers should consider a diagnosis of acute HIV infection in a person who has a suggestive clinical syndrome—especially those who report recent high-risk behavior (see Table 12).[7] Individuals may not

always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV acquisition. Thus, even in the absence of reported high-risk behaviors, practitioners should have a low threshold for considering a diagnosis of acute HIV infection, especially in high-prevalence areas (areas where ≥1% of people have HIV infection). Health care encounters in an emergency department create an opportunity to screen for acute or established HIV infection, as well as other sexually transmitted infections. Testing of remnant blood specimens from emergency departments identified acute HIV in approximately 1% of patients presenting with flu-like symptoms[8] and in 1% presenting for evaluation of possible mononucleosis with negative heterophile antibody tests.[9] A retrospective analysis of nine emergency departments in six U.S. cities using a laboratory-based, fourth generation antigen-antibody screening algorithm found that a new HIV diagnosis was made in 0.4% of 214,524 adolescents and adults screened. Among those with newly diagnosed HIV, 14.5% had acute HIV infection.[10] Current statistics on the prevalence of HIV in geographical areas in the United States can be found at these websites: AIDSVu and the Centers for Disease Control and Prevention (CDC)'s AtlasPlus.

Acute HIV infection is usually defined as detectable HIV RNA or p24 antigen in serum or plasma in the setting of a negative or indeterminate HIV antibody test result.[7,11] Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV p24 antigen (Ag/Ab assay) are now the preferred initial HIV screening test,[12] primarily due to their enhanced ability to detect acute HIV infection. The recommended laboratory testing algorithm is initiated using an HIV-1/2 Ag/Ab assay for HIV screening. Specimens that are reactive on an initial Ag/Ab assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial assay and have either negative or indeterminate antibody differentiation test results should be tested for quantitative or qualitative HIV RNA; an undetectable HIV RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV RNA in this setting indicates that acute HIV infection is highly likely.[13] HIV infection should be confirmed by repeat quantitative HIV RNA test or subsequent testing to document HIV antibody seroconversion. Persons receiving antiretroviral therapy (ART) during acute or very early HIV infection may demonstrate weaker reactivity to screening antibody assays or incomplete HIV antibody evolution; remain non-reactive to confirmatory antibody assays; and in the setting of sustained virologic suppression, may have complete or partial seroreversion.[14-18] Persons who acquire HIV while taking PrEP may sometimes also have ambiguous HIV test results. Options for confirming HIV infection and managing such cases is an area of evolving science recently summarized by CDC.[19] Clinicians seeking urgent advice can contact the Clinical Consultation Center's PrEP Service at 1-855-HIV-PREP.

Some health care facilities may still be using HIV testing algorithms that only recommend testing for anti-HIV antibodies. In such settings, when acute HIV infection is suspected in a patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV RNA test result indicate that acute HIV infection is highly likely. Providers should be aware that a low-positive quantitative HIV RNA level (e.g., <10,000 copies/mL) may represent a false-positive result, because HIV RNA levels in acute infection are generally (but not always) very high (e.g., >100,000 copies/mL).[1,2,4] Therefore, when a low-positive quantitative HIV RNA test result is obtained, the HIV RNA test should be repeated using a different specimen from the same patient, because repeated false-positive HIV RNA tests are unlikely.[2] The diagnosis of HIV infection should be confirmed by subsequent documentation of HIV antibody seroconversion.

Treating Early HIV Infection

As in chronic HIV infection, the goal of ART during early HIV infection is to suppress plasma HIV RNA to undetectable levels **(AI)** and to prevent the transmission of HIV **(AI)**. Importantly, as with chronic infection, persons with early HIV infection must be willing and able to commit to life-long ART. Individuals who do not begin ART immediately should be maintained in care and every effort made to initiate therapy as soon as they are ready.

Clinical trial data regarding the treatment of early HIV infection are limited. However, a number of studies suggest that individuals who are treated during early infection may experience immunologic and virologic benefits.[20-32] In addition, early HIV infection is often associated with high viral loads and increased infectiousness,[33] and the use of ART at this stage of infection to achieve and maintain a viral load <200 copies/mL is expected to substantially reduce the risk of HIV transmission.[34-37]

The START and TEMPRANO trials evaluated the timing of ART initiation (see Initiation of Antiretroviral Therapy). Although neither trial collected specific information on participants with early infection, the strength of the overall results from both studies' and the evidence from the other studies described above strongly suggest that, whenever possible, persons with HIV should begin ART upon diagnosis of early infection.

Drug Resistance Testing in the Setting of Early HIV Infection

Prior to the widespread use of integrase strand transfer inhibitors (INSTIs), data from the United States and Europe demonstrated that transmitted virus may be resistant to at least one antiretroviral (ARV) drug in up to 16% of persons with HIV.[38,39] In one study, 21% of isolates from persons with acute HIV infection demonstrated resistance to at least one ARV drug, with transmitted resistance consistently most common to non-nucleoside reverse transcriptase inhibitors (NNRTIs).[40-42] Therefore, before initiating ART in a person with early HIV infection, a specimen should be sent for drug resistance testing, though treatment **should not be delayed** pending resistance test results. The test results should be used to modify the ARV regimen if necessary **(AII)**. The Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend routine genotype testing for INSTI resistance in treatment-naive persons given the low rate of transmitted INSTI resistance and high barrier to resistance of dolutegravir (DTG) and bictegravir (BIC), unless transmitted INSTI resistance is a concern **(AIII)**. However, with the increasing use of INSTIs in recent years, the rate of transmitted INSTI resistance has increased (from 0.8% to 1.1%, $P = 0.04$), indicating a need for ongoing population monitoring.[43,44]

Considerations for Preventing HIV Transmission During Early HIV Infection

Persons with early HIV usually have a higher viral load than those with chronic HIV, and therefore are at a higher risk of sexual transmission to others. Prompt initiation of ART and subsequent viral load suppression can substantially reduce HIV transmission. Sustained viral suppression to <200 copies/mL can prevent transmission to sexual partners. Individuals starting ART should use another form of prevention with sexual partners (e.g., condoms, PrEP for partners who are HIV negative, or sexual abstinence) for at least the first 6 months of treatment and until they have a documented viral load <200 copies/mL **(AII)**. Many experts would recommend confirming sustained suppression before assuming no risk of sexual transmission of HIV **(AIII)** (see Antiretroviral Therapy to Prevent Sexual Transmission of HIV).

Treatment Regimens for Early HIV Infection

ART should be initiated with one of the combination regimens recommended for persons with chronic HIV infection **(AIII)** (see What to Start). Providers should inform individuals starting ART of the importance of adherence to achieve and maintain viral suppression **(AII)**. If available, the results of ARV drug resistance testing or the resistance pattern of the source person's virus should be used to guide selection of the regimen. All persons of child-bearing potential should have a pregnancy test before initiating ART **(AIII)**.

If ART is to be initiated before the results of drug resistance and HLA-B*5701 testing are available, one of the following regimens are appropriate options **(AIII)**:

- DTG with (emtricitabine [FTC] or lamivudine [3TC]) plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF])
- BIC/TAF/FTC

- Boosted darunavir (DRV) with (FTC or 3TC) plus (TAF or TDF)

DTG is a good treatment option because transmission of DTG-resistant HIV is rare, and DTG has a higher barrier to resistance than raltegravir and elvitegravir. Based on data from *in vitro* studies and clinical trials in ART-naive participants, it is anticipated that BIC, like DTG, also has a high barrier to resistance. However, clinical data and experience defining the BIC barrier to resistance are relatively limited at this time.

Preliminary data from Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[45] Follow-up data, however, showed that the prevalence of NTDs in association with DTG exposure at conception is lower (0.3%), but still slightly higher than with non-DTG containing ARV regimens (0.1%).[46,47] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when in choosing an ART regimen.

A pharmacologically boosted protease inhibitor (PI)-based regimen (e.g., boosted DRV) is also an option, as resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. Abacavir/3TC is not recommended as part of an empiric treatment of acute HIV infection unless the patient is known to be HLA-B*5701 negative—information that is seldom available when individuals with acute infection present for care. Therefore, TDF/FTC or TAF/FTC is generally recommended as a backbone in this setting. Baseline laboratory testing recommended for individuals with chronic HIV infection should be performed (see Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy). Individuals with HBV/HIV coinfection should remain on TDF/FTC or TAF/FTC as part of their ART regimen.

Given the increasing use of TDF/FTC as pre-exposure prophylaxis (PrEP) in individuals who are HIV negative,[48-50] early infection may be diagnosed in some persons while they are taking TDF/FTC for PrEP. In this setting, drug resistance results are particularly important; however, the regimens listed above remain as reasonable treatment options pending resistance testing results.

Treatment Regimens for Early HIV Infection During Pregnancy

All individuals of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII)**. Because early HIV infection, especially in the setting of high-level viremia, is associated with a high risk of perinatal transmission, all pregnant individuals with HIV should start combination ART as soon as possible to prevent perinatal transmission. Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Follow-Up After ART Initiation

After ART initiation, testing for plasma HIV RNA levels and CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy (e.g., HIV RNA testing 2 to 8 weeks after ART initiation, then every 4 to 8 weeks until viral suppression, and thereafter, every 3 to 4 months) **(AII)**.

Table 12. Identifying, Diagnosing, and Treating Acute and Recent HIV Infection

Suspicion of Acute HIV Infection:

- Health care providers should consider the possibility of acute HIV infection in individuals with the signs, symptoms, or laboratory findings described below, and recent (within 2 to 6 weeks) high risk of exposure to HIV.[a]
  - Signs, symptoms, or laboratory findings of acute HIV infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation.
  - High-risk exposures include sexual contact with a person who has HIV or a person at risk of HIV infection; sharing needles and syringes to inject drugs, as well as equipment used to prepare drugs for injection; or any exposure in which an individual's mucous membranes or any breaks in the skin come in contact with bodily fluid that potentially carries HIV.

Differential Diagnosis:

- The differential diagnosis of acute HIV infection may include but is not limited to viral illnesses such as EBV and non-EBV (e.g., CMV) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis. Diagnosis of any STI should prompt HIV testing and consideration of acute or early HIV infection.

Testing to Diagnose/Confirm Acute HIV Infection:

- Acute HIV infection is defined as detectable HIV RNA or p24 antigen (the specific antigen used in currently available HIV-1/2 Ag/Ab combination assays) in the setting of a negative or indeterminate HIV antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV infection is suspected requires plasma HIV RNA testing to diagnose acute HIV infection.
- A positive result on a quantitative or qualitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. In this case, the diagnosis of HIV infection should be later confirmed by subsequent documentation of HIV antibody seroconversion.

ART After Diagnosis of Early HIV Infection:

- ART is recommended for all individuals with HIV, including those with early[a] HIV infection **(AI)**. ART should be initiated as soon as possible after HIV diagnosis **(AII)**.
- Once initiated, the goals of ART are to achieve sustained plasma virologic suppression and to prevent HIV transmission **(AII)**.
- All individuals of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII)**.
- Pregnant individuals with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV **(AI)**.
- A blood sample for genotypic drug resistance testing should be obtained before initiation of ART to guide the selection of the regimen **(AII)**, but ART should be initiated as soon as possible, often before resistance test results are available. If resistance is subsequently identified, treatment should be modified as needed.
- ART can be initiated before the results of drug resistance testing are known. In this setting, one of the following ART regimens is recommended **(AIII)**:
  - DTG with (TAF or TDF)[b] plus (FTC or 3TC)
  - BIC/TAF/FTC
  - Boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC)
- Pregnancy testing should be performed in individuals of childbearing potential before initiation of ART **(AIII)**.
- Preliminary data from Botswana suggested that there is an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.[45] Follow-up data, however, showed that the prevalence of NTDs in association with DTG exposure at conception is lower (0.3%), but still slightly higher than with non-DTG containing ARV regimens (0.1%).[46,47] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.

[a] In some settings, behaviors that increase the risk of HIV infection may not be recognized or perceived as risky by the health care provider or the patient, or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV infection.

[b] TAF and TDF are two forms of TFV that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; Ag/Ab = antigen/antibody; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CMV = cytomegalovirus; DRV = darunavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; STI = sexually transmitted infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

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Adolescents and Young Adults with HIV (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations
• Adolescents living with HIV largely belong to two distinct groups—those who acquired HIV in infancy and are heavily antiretroviral therapy (ART)-experienced, and those who acquired HIV more recently during their teens.
• ART is recommended for all individuals with HIV **(AI)** to reduce morbidity and mortality and to prevent HIV transmission. Therefore, ART is also recommended for ART-naive adolescents.
• Before initiation of therapy, adolescents' readiness and ability to adhere to therapy within their psychosocial context need to be carefully considered as part of therapeutic decision making **(AIII)**.
• Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression **(AII)**.
• Data from an observational study in Botswana suggest that there may be an increased risk of neural tube defects in infants born to individuals who were receiving dolutegravir at the time of conception. Before initiating an integrase strand transfer inhibitor-based regimen in an adolescent of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.
• The adolescent sexual maturity rating (SMR) can help guide regimen selection when initiating or changing an ART regimen as recommended by either the Adult and Adolescent Antiretroviral Guidelines or the Pediatric Antiretroviral Guidelines. The Adult and Adolescent Aniretroviral Guidelines are more appropriate for postpubertal adolescents (i.e., those with SMRs of 4 or 5) **(AIII)**.
• Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings. Adult providers should be sensitive to the challenges associated with such transitions, consulting and collaborating with adolescent HIV care providers to ensure adolescents' successful transition and continued engagement in care **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Older children and adolescents now make up the largest percentage of children with HIV who receive care at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 26% of the approximately 50,000 people with newly diagnosed HIV in 2010 were youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% were among young men who have sex with men (MSM).[1] Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV.[1] Trends in HIV/AIDS prevalence indicate that the disproportionate burden of HIV among racial minorities is even greater among minority youth aged 13 to 24 years than among those older than 24 years.[2] Furthermore, trends for all HIV diagnoses among adolescents and young adults decreased or remained stable for all transmission categories except among young MSM in 46 states and five U.S.-dependent areas from 2007 to 2010. Adolescents with HIV represent a heterogeneous group in terms of socio-demographics, mode of HIV acquisition, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications to use.

Most adolescents who acquire HIV do so through sex. Many of them have recently acquired HIV and are unaware of their HIV status. Many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage to and engagement in care, and initiation of ART.[3] High-grade viremia was reported in a cohort of youth living with HIV who were identified by adolescent HIV specialty clinics in 15 major metropolitan U.S. cities. The mean HIV viral load for the cohort was 94,398 copies/mL; 30% of the youth were not successfully linked to care.[4] In a study of youths with

recent HIV infection, as determined by the detuned antibody testing assay strategy, which defined recent infection as occurring within 180 days of testing, primary genotypic resistance mutations were reported in 18% of the youths.[5] In an ARV treatment trial, a cohort of ART-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance.[6] As these youth were naive to all ARV drugs, these results reflect transmission of resistant virus. This transmission dynamic indicates that a substantial proportion of the study participants' sexual partners were likely to be older and ART-experienced; thus, it is imperative that clinicians use baseline resistance testing to guide initial therapy in youth who have recently acquired HIV and who are naive to ART.

A limited but increasing number of adolescents with HIV are long-term survivors of HIV that was acquired perinatally or in infancy through blood products. These adolescents are usually heavily ART-experienced and may have a unique clinical course that differs from that of adolescents who acquire HIV later in life.[7] Adolescents who acquired HIV perinatally or in infancy often initiated ART early in life with mono- or dual-therapy regimens, resulting in incomplete viral suppression and emergence of viral resistance. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be selected using the same guiding principles used for heavily ART-experienced adults (see Virologic Failure).

Developmentally, adolescents are at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity compete with their concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and need to fit in with their peers. This makes it challenging to sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage and retain adolescents in care so they can improve and maintain their health for the long term.

Given the challenges of retaining youth in care and achieving long-term viral suppression,[8] more intensive case management approaches may be considered for adolescents with HIV.[9,10] Adolescents may seek care in several settings, including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.[11] When available, youth services may help enhance HIV care engagement and retention among adolescents.[12] Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.[11]

Antiretroviral Therapy Considerations in Adolescents

The START and TEMPRANO trials are discussed elsewhere in these guidelines (see Initiation of Antiretroviral Therapy).[13,14] The results of these trials supported the initiation of ART in all individuals who are able and willing to commit to treatment, and who can understand the benefits and risks of therapy and the importance of excellent adherence.[13,14] Neither of these trials included adolescents; however, the recommendations that were developed using the data from these trials apply to adolescent patients as well as adult patients. Adolescents are expected to derive benefits from early ART initiation that are similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of American youth with HIV, their ability to adhere to therapy needs to be carefully considered as part of therapeutic decision making. Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR; also known as the Tanner stage) can be helpful when ART initiation is being considered for this population (see this SMR table from the World Health Organization). Adult guidelines for ART initiation (see What to Start) or regimen changes are usually appropriate for postpubertal adolescents (SMR 4 or 5) because the clinical course of HIV infection in postpubertal adolescents who acquired HIV sexually or through injection drug use during adolescence is more similar to that in adults than that in children. Adult guidelines can also be useful for postpubertal youth who acquired HIV perinatally and whose long-term HIV infection has not affected their sexual maturity (SMR 4 or 5).

Pediatric guidelines for ART may be more appropriate for adolescents who acquired HIV during their teen years (e.g., through sex) but who are sexually immature (SMR 3 or less), and for adolescents who acquired HIV perinatally with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other comorbidities (SMR 3 or less; see What to Start in the Pediatric Antiretroviral Guidelines).

Postpubertal youth who acquired HIV perinatally often have treatment challenges associated with the long-term use of ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects (see Virologic Failure, Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression, and Adverse Effects of Antiretroviral Agents). Postpubertal adolescents who acquired HIV perinatally may also have comorbid cognitive impairments that compound adherence challenges that are common among youth.[15]

Dose of ARV drugs should be prescribed according to the patient's SMR and not solely based on age. Adolescents in early puberty (SMR 3 or less) should be administered doses on pediatric schedules, whereas those in late puberty (SMR 4 or 5) should follow adult dosing schedules. However, SMR and age are not necessarily directly predictive of drug pharmacokinetics (PKs). Because puberty may be delayed in children with perinatally acquired HIV,[16] continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Data are lacking on the optimal doses for each ARV drug for this group of children; therefore, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered when determining when to transition youth from pediatric to adult doses. Youth who are in their growth spurt period (i.e., SMR 3 in females and SMR 4 in males) and who are following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in these circumstances to help guide therapy decisions. PK studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see the Pediatric Antiretroviral Guidelines.

Preliminary data from a study in Botswana reported an increased prevalence of neural tube defects (NTDs) among infants born to women who were receiving dolutegravir (DTG) at the time of conception; the prevalence of NTDs in these infants was found to be 0.9%.[17,18] Follow-up data showed that the prevalence of NTDs in infants who had been exposed to DTG at conception was lower than originally reported (0.3%), but still higher than the prevalence in infants who were exposed to ARV regimens that did not contain DTG (0.1%).[19,20] There are insufficient safety data on the use of bictegravir (BIC) at the time of conception and during pregnancy to determine whether it is safe to use. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**. Before initiating an integrase strand transfer inhibitor-based regimen in an adolescent of childbearing potential, clinicians should review the information in Table 6b.

Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Adherence Concerns in Adolescents

Adolescents with HIV are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. To meet the medical and psychosocial needs of adolescents with HIV, who frequently lack both health insurance and experience with health care systems, comprehensive systems of care are required. Studies of adolescents who acquired HIV during their teen years and adolescents with perinatal acquisition demonstrate that many adolescents in both groups face numerous barriers to adherence.[21-23] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[24] Reasons that adolescents with HIV often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV diagnosis;

- Misinformation;
- Distrust of the medical establishment;
- Fear of ART and lack of confidence in the effectiveness of medications;
- Low self-esteem;
- Unstructured and chaotic lifestyles;
- Mood disorders and other mental illness;
- Lack of familial and social support;
- Lack of or inconsistent access to care or health insurance; *and*
- Risk of inadvertent disclosure of their HIV status if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with a realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, timers, and pill boxes) that are stylish and/or inconspicuous.[25] In a randomized controlled study among nonadherent youth aged 15 years to 24 years, youth who received medication reminders through their cell phones demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls.[26] It is important to make medication adherence user-friendly and to avoid HIV-related stigma as much as possible for the older child or adolescent. Adolescents may not understand the importance of taking medications when they are asymptomatic, particularly when the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.[27-29] Directly observed therapy may be considered for some adolescents with HIV, such as those with mental illness.[30-34]

Difficult Adherence Problems

Predicting long-term adherence in an adolescent can be very challenging because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style. A young person's ability to adhere to therapy needs to be considered as part of therapeutic decision-making. Erratic adherence may result in the development of resistance mutations, which can limit future regimen options. Clinicians who care for adolescents with HIV frequently manage youth who pose significant concerns regarding their ability to adhere to therapy. In these cases, the following strategies can be considered:

- A short-term deferral of ART until adherence is more likely or while adherence-related problems are aggressively addressed;
- An adherence testing period in which a placebo (e.g., vitamin pill) is administered; *and*
- The avoidance of any regimens with low resistance barriers.

Such decisions should ideally be individualized to reflect each patient's clinical status. For a more detailed discussion on specific therapy and adherence issues for adolescents with HIV, see Adherence to the Continuum of Care and the Pediatric Antiretroviral Guidelines.

Other Considerations in Adolescents

All adolescents should be screened for sexually transmitted infections (STIs), especially human papilloma virus (HPV). In young MSM, screening for STIs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.[35] For a more detailed discussion on STIs, see the most recent CDC guidelines,[36] the Adult and Adolescent Opportunistic Infection Guidelines, and the Pediatric Opportunistic Infection Guidelines on HPV among adolescents with HIV.

Family planning counseling, including a discussion of the risks of perinatal HIV transmission and methods to reduce those risks, should be provided to all youth. Providing gynecologic care for female adolescents with

HIV is especially important. Choice of ART may also be affected by a patient's potential for pregnancy and choice of contraception, since some ARV drugs can interact with hormonal contraceptives (see Drug-Drug Interactions).

Finally, transgender youth with HIV represent an important population that requires additional psychosocial and health care considerations. For a more detailed discussion, see Adolescent Trials Network Transgender Youth Resources.

Transitioning Care

HIV is a lifelong infection that requires treatment through several stages of growth and development; therefore, HIV care programs and providers need to be flexibile in order to appropriately transition care for children, adolescents, and young adults with HIV. A successful transition requires an awareness of the fundamental differences between many adolescent and adult HIV care models.

In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referring the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considering areas such as access to medical insurance; the adolescent's degree of independence/autonomy and decisional capacity; patient confidentiality; and informed consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less-motivated patients.

As an additional complication to this transition, adolescents with HIV belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial needs:

- Adolescents who acquired HIV perinatally. These adolescents are likely to have longer histories of disease burden, complications, and chronicity; less functional autonomy; a greater need for ART; and higher mortality risks.
- Youth who more recently acquired HIV during their adolescence. These adolescents are likely to be in earlier stages of HIV infection and have higher CD4 T lymphocyte cell counts; they are also less likely to have drug resistance mutations and may benefit from simpler treatment regimens.

Interventions to facilitate transition should be implemented early to ensure a successful transition.[37] These interventions include the following:

- Developing an individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between adolescent clinics and adult clinics;
- Identifying adult care providers who are willing to care for adolescents and young adults;
- Addressing patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles;
- Helping youth develop life skills, including counseling them on the appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and the importance of self-efficacy in managing medications, insurance, and assistance benefits;
- Identifying an optimal clinic model based on specific needs (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Implementing ongoing evaluation to measure the success of a selected clinic model;
- Engaging adult and adolescent care providers in regular multidisciplinary case conferences;
- Implementing interventions that may improve outcomes, such as support groups and mental health

consultation;

- Incorporating a family planning component into clinical care; *and*
- Educating HIV care teams and staff about transitioning.

Discussions regarding transition should begin early, before the actual transition process.[38] Attention to the key interventions noted above will likely improve adherence to appointments and allow the youth to be retained in care.

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HIV-2 Infection (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and lower mortality rate than HIV-1 infection. However, progression to AIDS and death will occur in the majority of individuals without treatment.
- No randomized controlled trials have addressed when a person with HIV-2 should start antiretroviral therapy (ART) or which regimens are most effective for initial or second-line ART when treating HIV-2; thus, the optimal treatment strategy is not well defined.
- Existing data on the treatment of HIV-2, and extrapolation from data on the treatment of HIV-1, suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others **(AIII)**.
- Quantitative plasma HIV-2 RNA viral load testing for clinical care is available and should be performed before initiation of ART **(AIII)**.
- HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; therefore, these drugs **should not be included** in ART regimens for HIV-2 infection **(AII)**.
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**.
- Initial ART regimens for ART-naive patients who have HIV-2 mono-infection or HIV-1/HIV-2 coinfection should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AII)**. An alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs **(BII)**.
- HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response **(AIII)**. Unlike persons with HIV-1, persons with HIV-2 should continue to undergo periodic CD4 count testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load.
- Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in persons with HIV-2 while they are on ART. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are approved for clinical use.
- In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Overview

HIV-2 infection is endemic in West Africa, with certain countries experiencing a population prevalence of >1%. The possibility of HIV-2 infection should be considered when treating persons of West African origin, persons who have had sexual contact with or who have shared needles with persons of West African origin, and persons who reside in countries with strong socioeconomic ties to West Africa (e.g., France, Spain, Portugal, and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India). Globally, it has been estimated that one million to two million individuals have HIV-2, a number that includes people with HIV-1/HIV-2 dual infection. However, current and accurate prevalence data are scarce, and neither the Joint United Nations Programme on HIV and AIDS nor the World Health Organization have formal surveillance systems for HIV-2.[1]

Clinical Course of HIV-2 Infection

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and a lower mortality rate than HIV-1 infection.[2,3] However, without effective antiretroviral therapy (ART), HIV-2 infection will progress to AIDS and death in the majority of individuals.[4] Concomitant HIV-1 and HIV-2 infection may occur, and the possibility of this coinfection should be considered when treating persons from areas with a high prevalence of HIV-2.

Diagnostic and Monitoring Assays for HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in persons who have clinical conditions that suggest HIV infection but who have atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).[5] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in persons who have serologically confirmed HIV infection but who have low or undetectable HIV-1 RNA levels, or in those who have declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on ART.

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[6] recommend using an HIV-1/HIV-2 antigen/antibody combination immunoassay for initial testing and using an HIV-1/HIV-2 antibody differentiation immunoassay for subsequent testing. The Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories) is approved by the Food and Drug Administration (FDA) to differentiate HIV-1 infection from HIV-2 infection. The Multispot HIV-1/HIV-2 Rapid Test is no longer available. Commercially available HIV-1 RNA assays do not reliably detect or quantify HIV-2 RNA.[7] Quantitative HIV-2 RNA testing is available at the University of Washington (UW)[8] and the New York State Department of Health (NYSDOH).[9] HIV-2 nucleic acid amplification test-based (total DNA/RNA) diagnostic testing is available for clinical care at UW.[10] However, it is important to note that up to one-third of persons with untreated HIV-2 will have HIV-2 RNA levels below the limits of detection (10 copies/mL for UW testing and 7 IU/mL for NYSDOH testing); some of these persons will have clinical progression and CD4 count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are approved by the FDA for clinical use. HIV-2 genotypic ARV resistance assays are available at UW for research use only.

Treatment of HIV-2 Infection

To date, no randomized controlled trials that address when to start ART or the choice of initial or subsequent ART regimens for HIV-2 have been completed;[11] thus, the optimal treatment strategy has not been defined. Existing data on the treatment of HIV-2 and extrapolation from data on the treatment of HIV-1 suggest that ART should be started at or soon after HIV-2 diagnosis in order to prevent disease progression and transmission of HIV-2 to others **(AIII)**. However, CD4 cell recovery in persons with HIV-2 who are on ART is generally poorer than that observed in persons with HIV-1.[12,13]

Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs); however, HIV-2 is more likely to develop resistance to NRTIs than HIV-1.[14] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs);[15] thus, NNRTI-based regimens **are not recommended** for treatment of HIV-2 **(AII)**. Several small studies in individuals with HIV-2 have reported poor responses to dual-NRTI regimens[16,17] or regimens that contain an NNRTI plus two NRTIs.[18,19] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[20,21]

Integrase strand transfer inhibitor (INSTI)-based regimens or protease inhibitor (PI)-based regimens are treatment options for persons with HIV-2. As discussed below, two single-arm clinical trials showed favorable outcomes in patients who received INSTI-based regimens; data regarding the efficacy of PI-based regimens primarily come from observational reports. A randomized controlled trial comparing raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to lopinavir/ritonavir plus TDF/FTC is currently underway (FIT-2; NCT02150993).

Integrase Strand Transfer Inhibitor-Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), and bictegravir—have potent activity against HIV-2 *in vitro*.[22-26] INSTI-based regimens have shown favorable treatment responses in observational studies.[27-29] Two single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. One study evaluated RAL plus TDF/FTC, and the other evaluated EVG/cobicistat/TDF/FTC. Both studies demonstrated favorable clinical and immunovirologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.[30,31]

Protease Inhibitor-Based Regimens

In general, regimens that contain boosted PIs that are active against HIV-2 (and that also include two NRTIs) have resulted in more favorable virologic and immunologic responses than regimens that consist of only two or three NRTIs.[12,13,21,32] Darunavir (DRV), lopinavir, and saquinavir are more active against HIV-2 than other approved PIs.[33-35] Older, unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.[11,16,17,36,37]

Amongst the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[38] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates;[39] however, there are no FDA-approved assays that can determine HIV-2 co-receptor tropism, and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[40] There are no data yet on the activity of ibalizumab against HIV-2.

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection;[41-44] however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

Until there are more definitive data on outcomes, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends the following regimens for individuals with HIV-2 mono-infection or HIV-1/HIV-2 dual infection:

- A regimen that contains one INSTI plus two NRTIs is the recommended initial ART regimen for most individuals with HIV-2 **(AII)**. Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects in infants born to those who were receiving DTG at the time of conception; however, the risk of these defects is still low. Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.
- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII)**.
- NNRTI-based regimens **are not recommended** for persons with HIV-2 **(AII)**.
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**. See Hepatitis B Virus/HIV Coinfection for more information.
- HIV-2 plasma RNA levels, CD4 cell counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII)**.
- Persons who have HIV-2 RNA levels that are below the limits of detection before they initiate ART should still undergo routine HIV-2 plasma RNA monitoring in addition to CD4 cell count and clinical monitoring. Unlike HIV-1, persons with HIV-2 require continued CD4 cell count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII)**.

Persons with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as those with HIV-1 (see What to Start). There are no data on HIV-2 treatment as prevention; however, both data from studies of people with HIV-1 and data on the natural history of HIV-2 transmission suggest that effective ART likely provides a reduced risk of transmission to sexual partners.

Viral mutations that are associated with resistance to NRTIs, PIs, and/or INSTIs may develop in persons with HIV-2 while they are on ART.[35,45,46] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[47,48] In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some persons with HIV-2 who had extensive ART experience and RAL resistance.[49-52] Genotypic algorithms that are used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because the pathways and mutational patterns that lead to resistance may differ between the HIV types (see the HIV2EU Algorithm and the Stanford University HIV Drug Resistance Database).[53] In the event of

virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.

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HIV and the Older Person (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations When Caring for Older Persons With HIV

- Antiretroviral therapy (ART) is recommended for all people with HIV regardless of CD4 T lymphocyte cell count **(AI)**. ART is especially important for older individuals because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART.
- Given that the burden of aging-related diseases is significantly higher among persons with HIV than in the general population, additional medical and social services may be required to effectively manage both HIV and comorbid conditions.
- Adverse drug events from ART and concomitant drugs may occur more frequently in older persons with HIV than in younger individuals with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, cognitive, and liver health of older individuals with HIV should be monitored closely.
- Polypharmacy is common in older persons with HIV; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications.
- The decline in neurocognitive function with aging is faster in people with HIV than in people without HIV. HIV-associated neurocognitive disorder (HAND) is associated with reduced adherence to therapy and poorer health outcomes including increased risk of death. For persons with progressively worsening symptoms of HAND, referral to a neurologist for evaluation and management or a neuropsychologist for formal neurocognitive testing may be warranted **(BIII)**.
- Mental health disorders are a growing concern in aging people with HIV. A heightened risk of mood disorders including anxiety and depression has been observed in this population. Screening for depression and management of mental health issues are critical in caring for persons with HIV.
- HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older persons with HIV and complex comorbidities.
- Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of older people with HIV

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Effective antiretroviral therapy (ART) has increased survival in individuals with HIV,[1,2] resulting in an increasing number of older individuals living with HIV. In the United States, from 2012 through 2017, the annual fraction of persons newly diagnosed with HIV aged ≥50 years was stably 17%.[3] Among persons with HIV at year-end 2016, 48% were aged ≥50 years, 8% were aged ≥65 years, and trends suggest that these proportions will increase steadily.[3] Care of people with HIV will increasingly involve adults aged ≥60 years, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited. The discussion in this section of the guidelines refers to individuals aged ≥50 years as older persons with HIV.

There are several distinct areas of concern regarding aging and HIV.[4] First, older persons with HIV may suffer from aging-related comorbid illnesses and require substantially more non-ART medications[5] than younger people, which may complicate HIV clinical care.[6] Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with more advanced age. Third, reduced mucosal and immunologic defenses (e.g., postmenopausal atrophic vaginitis) and changes in risk related-behaviors (e.g., decrease in condom use because of less concern about pregnancy or more high-risk sexual activity with increased use of erectile dysfunction drugs) in older adults may lead to increased risk of acquisition and transmission of HIV.[7,8] Finally, HIV screening among older adults remains low because they are generally perceived to be at low risk of acquiring HIV.

HIV Screening and Diagnosis in the Older Person

Failure to consider a diagnosis of HIV has likely contributed to later initiation of ART in older persons with HIV.[9] The Centers for Disease Control and Prevention (CDC) estimates that in 2016, 36% of adults aged ≥55 years met the case definition for AIDS at the time of HIV diagnosis. The comparable CDC estimates are 16% for adults aged 25 to 34 years and 27% for adults aged 35 to 44 years.[10] In one observational cohort, older people (defined as those aged ≥35 years) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion and steeper CD4 count decline over time,[11] and tended to present to care with significantly lower CD4 counts.[12] When individuals aged >50 years present with severe illnesses, HIV and AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Although many older individuals engage in risk behaviors associated with acquisition of HIV, they may see themselves or be perceived by providers as at low risk of infection and, as a result, they are less likely to be tested for HIV infection than younger persons.[13,14] Despite CDC guidelines recommending HIV testing at least once for individuals aged 13 to 64 years, and more frequently for those at risk,[15] HIV testing prevalence remains low (<5%) among adults aged 50 to 64 years, and decreases with increasing age.[16] Clinicians must be attuned to the possibility of HIV infection in older adults, including those aged ≥64 years, especially in those who may engage in high-risk behaviors. Sexual history taking and screening for other risk factors (e.g., injection drug use) that may place older adults at risk of HIV infection are therefore an important component of general health management for older adults. Risk-reduction counseling, and screening for HIV and sexually transmitted infections should be done, if indicated. Older adults who are at risk of acquiring HIV should be counseled on comprehensive HIV prevention strategies, including the option of HIV pre-exposure prophylaxis (PrEP). Age alone should not exclude older adults from being evaluated for and offered PrEP (refer to CDC PrEP Guidelines for details).

Impact of Age on HIV Disease Progression

HIV infection in older persons presents unique challenges and these challenges may be compounded by ART:

- Chronic HIV infection is associated with elevated cellular and soluble markers of immune activation and inflammation. Although these levels decline with ART, they remain higher than normal, even with suppressive ART. Levels of these markers also increase with aging, and the rate of this age-related change was demonstrated to be faster in people with HIV with viremia than in those with virologic suppression on ART and in people without HIV.[17]
- HIV infection may induce immuno-phenotypic changes akin to accelerated aging, with senescent T cells which in older persons have been associated with negative outcomes including frailty and cardiovascular disease.[4,18-21] Some studies have shown that people with HIV may exhibit chromosomal and immunologic features similar to those induced by aging, such as the accumulation of highly differentiated $CD28^{-}/CD57^{+}$ $CD8^{+}$ T cells commonly used as markers of immunosenescence.[22-24] However, other studies show the immunologic changes in HIV to be distinct from age-related changes.[25] Cytomegalovirus (CMV) infection is very prevalent among people with HIV, and as they age, immune response to CMV—rather than HIV—may play a pivotal role in immunosenescence observed even in people with virologic suppression.[26]
- Although data on the increased incidence and prevalence of age-associated comorbidities in people with HIV are accumulating,[27,28] the age at diagnosis for myocardial infarction, stroke, and non-AIDS cancers in people with and without HIV is the same.[28,29]
- As the life expectancy of persons living with HIV increases with ART, more cisgender women with HIV are experiencing menopause. Although menopause may occur earlier in cisgender women with HIV than in cisgender women in the general population,[30] early menopause may also be a consequence of smoking, depression, substance use, and other psychosocial factors that are disproportionately present in cisgender women with HIV.[31]

- Older persons with HIV have a greater incidence of health complications and comorbidities than adults of a similar age who do not have HIV, and may exhibit a frailty phenotype (defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity) earlier and in greater proportions than the general population.[32,33] Frailty in persons with HIV has been associated with adverse outcomes including incident cardiovascular disease, diabetes mellitus, recurrent falls and fractures, lower quality of life scores, cognitive impairment, hospitalization, and mortality.[34-43] Cisgender women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.[34,44-46] Although the frailty phenotype is still incompletely characterized in people with HIV, its early recognition may lead to targeted interventions to improve the wellbeing of this population.[43]

Antiretroviral Therapy in the Older Person with HIV

Importance of Early Treatment Initiation

ART is recommended for all individuals with HIV (**AI**; see Initiation of Antiretroviral Therapy). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population.[47,48] In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (people aged 45 to 65 years).[49] This was demonstrated in an analysis of HIV cohorts from Europe and the Americas showing a lower all-cause and non-AIDS mortality with immediate ART initiation in people aged 50 to 70 years.[50] It was also seen in a START substudy in which persons aged >50 years were among the groups that experienced the greatest risk reduction when ART was started when CD4 counts were >500 cells/mm^3.[51] All older persons with HIV should be informed that maintaining a plasma HIV RNA (viral load) at <200 copies/mL with ART improves overall health and prevents sexual transmission of HIV.

Choice of Antiretroviral Regimens in the Older Person with HIV

The choice of antiretroviral (ARV) regimen for an older person with HIV should be informed by a comprehensive review of the person's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an ARV regimen based on a person's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older persons with HIV and reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix B, Table 10). In addition, ARV regimen selection may be influenced by potential interactions between ARV medications and drugs used concomitantly to manage comorbidities (see Tables 21a-22b). Adults aged >50 years should be monitored for ART effectiveness and safety as similarly recommended for other populations with HIV (see Table 3); however, in older persons, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, central nervous system, metabolic, and bone health (see Table 17). ART regimens that contain tenofovir disoproxil fumarate (TDF), boosted protease inhibitors (PIs), or both are associated with a significantly greater loss of bone mineral density than regimens containing other NRTIs and integrase strand transfer inhibitors (INSTIs).[52-55] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide may be considered as alternatives to the use of TDF in older individuals who may be at risk of osteopenia or osteoporosis; however, with ABC, the benefit should be balanced with potentially increasing risk of cardiovascular disease.

Antiretroviral Efficacy and Safety Considerations in the Older Person with HIV

The efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART differs in older and younger people. In an observational study, a higher rate of viral suppression was seen in people aged >55 years than in younger people.[56] However, ART-associated CD4 cell recovery in older adults is generally slower and

lower in magnitude than in younger people;[12,57-59] suggesting that starting ART at a younger age may result in better immunologic response and possibly clinical outcomes.

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney functions decrease with age and may result in impaired drug elimination and increased drug exposure.[60] Most clinical trials have included only a small proportion of participants aged >50 years, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Because it is unknown whether drug accumulation in the older person may lead to greater incidence and severity of adverse effects than seen in younger persons, therapy in older persons requires close monitoring and heightened awareness of drug-related adverse outcomes.

Impact of Comorbidities and Polypharmacy in Older Persons with HIV

People with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management.[5] In addition to taking medications to manage HIV infection and comorbid conditions, many older persons with HIV are also taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). Older individuals may also self-medicate with over-the-counter medicines or supplements.

Polypharmacy is more common in older persons with HIV than similarly aged persons in the general population.[5,61-63] In one large cohort of older patients with HIV in France, 62% of those whose HIV was diagnosed before 2000 had one or more comorbidities, and 70% were receiving at least one comedication.[64] Among persons living with HIV aged ≥65 years, the prevalence of comorbidities and polypharmacy rose with increasing age and duration of HIV infection.[65]

In older persons without HIV, polypharmacy is a major cause of iatrogenic complications.[66] Some of these complications may be caused by medication errors (by prescribers or patients), medication nonadherence, additive drug toxicities, and drug-drug interactions. Older persons with HIV are probably at an even greater risk of polypharmacy-related adverse consequences than younger or similarly aged people without HIV. When evaluating any new clinical complaint or laboratory abnormality in people with HIV, especially in older persons, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug-Drug Interaction Concerns

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[67] Potential drug-drug interactions can occur between ARV and non-ARV medications, as well as between non-ARV medications.[63] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 21a-22b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of an interaction may be greater in older persons with HIV than in younger people with HIV; therefore, it is very important to remain vigilant to potential drug-drug interactions given the high prevalence of polypharmacy in older persons with HIV. In reviews of ARV and non-ARV medications prescribed for older persons with HIV, more than half of the medications had the potential for drug-drug interaction, including some severe interactions.[68,69] The risk is higher with PI-based ART than with INSTI-based ART.[68-70]

Adherence Concerns

Suboptimal adherence to ART is the most common cause of treatment failure. Complex dosing requirements, high pill burden, polypharmacy, inability to access medications because of cost or availability, limited health literacy (including misunderstanding of instructions), depression, and neurocognitive impairment are among the key reasons for nonadherence.[71] Although many of these factors associated with nonadherence

may be more prevalent in older persons with HIV, some studies have shown better adherence to ART among older persons than younger individuals.[72-74] Severe menopausal symptoms are also associated with reduced adherence to ART, which increases the risk of drug resistance and adverse HIV-related health outcomes in menopausal cisgender women.[75] Clinicians should regularly engage with older persons to identify any factors, such as neurocognitive deficits or hormonal changes, that may decrease adherence to ART. To facilitate medication adherence, it may be useful to discontinue unnecessary medications, simplify regimens, and recommend evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members (see Adherence to the Continuum of Care).

Optimizing Antiretroviral Therapy in Older Persons with HIV

Given the greater incidence of comorbidities, non-AIDS complications, and frailty among older people with HIV, switching one or more ARVs in an HIV regimen may be necessary to minimize toxicities and drug-drug interactions. For example, expert guidance now recommends bone density monitoring in men aged ≥50 years and postmenopausal cisgender women, and suggests switching from TDF or boosted PIs to other ARVs in older persons at high risk for fragility fractures.[76] Given the high prevalence and faster progression of chronic kidney disease in aging persons with HIV, likely from a combination of HIV, ART, and non-HIV risk factors, development of the disease in an older person on ART must be monitored with great vigilance.[77,78] In persons with HIV at risk for or with declining renal function, consideration should be given to avoiding regimens containing TDF and atazanavir.[79]

Interrupting or Discontinuing Antiretroviral Therapy in Older Persons with HIV

Few data exist on the use of ART in severely debilitated people with chronic, severe, or non-AIDS-related terminal conditions.[80,81] Withdrawal of ART usually results in rebound viremia and a decline in CD4 count. In addition, an acute retroviral syndrome after abrupt discontinuation of ART has been reported. Even in severely debilitated adults, most clinicians would continue therapy if there are no significant adverse reactions to the ARV drugs. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion of the risks and benefits of continuing or withdrawing treatment.

Non-AIDS HIV-Related Complications and Other Comorbidities in the Older Person with HIV

As AIDS-related morbidity and mortality have decreased among persons treated effectively with ART, non-AIDS conditions constitute an increasing proportion of serious illnesses among people with HIV.[82-84] The burden of age-related diseases is significantly higher among persons with HIV than in the general population, likely due to both traditional non-HIV-related and HIV-related factors.[85] Heart disease and cancer are the leading causes of death in older Americans.[86] Similarly, other non-AIDS events such as cognitive impairment, and liver disease have also emerged as major causes of morbidity and mortality in people with HIV receiving effective ART. Moreover, people with HIV are more likely to be current or former cigarette smokers than adults without HIV,[87] and model-based analyses have suggested that smoking cessation could improve life expectancy among older adults with HIV on ART.[88]

The prevalence of multimorbidity among persons with HIV has increased in the past decade,[89] with hypertension and hypercholesterolemia being the most common comorbidities. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging among adults with HIV.[90-92]

HIV-specific primary care guidelines have been developed and are available for clinicians caring for older persons with HIV.[93,94] Specific guidelines have also been developed for the evaluation and management of the following specific comorbidities in people with HIV: bone health,[76] kidney disease,[95] and cardiovascular disease.[96] In addition, the following guidelines recently developed for the general population can be applied

to the older persons with HIV: management of hyperglycemia[97] and hyperlipidemia.[98] However, it is important to note that the recommendations in these guidelines have not all been validated in the context of HIV disease. For instance, cardiovascular risk prediction functions developed for the general population likely underestimate the risk in persons with HIV.[99]

Neurocognitive Impairment and Mental Health Concerns in the Older Person with HIV

HIV-associated neurocognitive disorder (HAND), manifesting as difficulty with memory, attention, speed of information processing, and executive and motor functions, affects up to 30% of people with HIV on virally suppressive ART.[100] Though an accurate prevalence of neurocognitive impairment in older people with HIV is not yet available, the risk of HIV-associated brain injury and HAND appears to be higher with increasing age.[101-103] Neurocognitive function declines with increasing age in people with or without HIV, but the trajectory of the decline is steeper in individuals with HIV.[104] This accelerated decline is likely multifactorial, relating to injury associated with direct HIV effects in the brain, higher prevalence of comorbidities and coinfections, more severe vascular disease, mental health disorders, social isolation, and polypharmacy in this population.[105-107] Hormonal shifts that occur with aging may contribute to neurocognitive impairment, and these changes may manifest as unique differences in clinical manifestations by gender.[108] Finally, the risk of neurodegenerative disease rises with increasing age independent of HIV, and differentiating HAND from Alzheimer's disease or other forms of progressive dementia is now an important clinical concern.[109]

HAND carries potentially detrimental clinical consequences for aging people with HIV. In a prospective observational study, neurocognitive impairment was predictive of lower likelihood of retention in care among older persons.[110] HAND is also associated with reduced adherence to therapy[111] and poorer health outcomes including increased mortality.[112] Given the importance of cognitive health, screening for neurocognitive impairment is important, though optimal primary-care based screening methods are as yet unclear. Initial screening with questions regarding any symptoms of memory or concentration difficulties should be performed routinely, though individuals with substantial impairment may not have enough insight into their condition to answer the questions. No brief cognitive screening test has been clearly shown to be sensitive or specific for HAND; the frequently used Mini-Mental State Exam does not typically capture executive function impairment which is the main manifestation of subtle HAND.[113] The Montreal Cognitive Assessment may be more sensitive for HAND but is not specific. If a patient has persistent concerns over time, has symptoms corroborated by an acquaintance, or has progressively worsening symptoms, referral to a neurologist for evaluation and management or to a neuropsychologist for formal neuropsychological testing may be warranted **(BIII)**.

Mental health disorders are a growing concern in aging people with HIV, though little is known about their prevalence and consequences in this population specifically. In a study that compared a cohort of individuals aged >60 years with HIV to a historical control group of healthy older individuals, a heightened risk of mood disorders including anxiety and depression was noted among those with HIV.[114] Social isolation combined with depression is particularly common among older adults with HIV and, in addition to its direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.[115,116] The risk of suicide remains greater in people with HIV than in the general population, though increasing age may not further heighten the risk.[117] Screening for depression and management of mental health issues are critical aspects of HIV primary care; guidelines for people with HIV, as well as for aging individuals without HIV, recommend behavioral approaches including individual psychotherapy, cognitive behavioral therapy, and group therapy, and often pharmacological treatment.[118,119] Integrated care models with routine screening by health care support staff, review by primary providers, and referral to on-site mental health specialists are likely to be the most effective approaches in vulnerable aging populations.

Health Care Utilization, Cost Sharing, and End-of-Life Issues

The significantly increased burden of age-related comorbidities, including cardiovascular disease, chronic kidney disease, neurocognitive disease, and fractures, leads to a considerable increase in healthcare

utilization and higher costs.[120] Out-of-pocket health care expenses (e.g., copayments, deductibles), loss of employment, and other financial-related factors can cause temporary interruptions in treatment, including ART, which should be avoided whenever possible. The increased life expectancy and higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services[121] and require a focused approach to prioritize modifiable health-related problems.[122] Facilitating continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders. As with all aging people, it is important to discuss living wills, advance directives, and long-term care planning.

Conclusion

HIV infection can be overlooked in aging adults who tend to present with more advanced disease and experience accelerated CD4 loss. HIV induces immune-phenotypic changes that have been compared to accelerated aging. Effective ART has prolonged the life expectancy of people with HIV, increasing the number of adults aged >50 years living with HIV. However, unique challenges in this population include greater incidence of health complications and comorbidities, some of which may be exacerbated or accelerated by long-term use of some ARV drugs. Providing comprehensive multidisciplinary medical and psychosocial support to patients and their families (the "Medical Home" concept) is of paramount importance in the aging population. Continued involvement of HIV experts, geriatricians, and other specialists in the care of older persons with HIV is warranted.

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Substance Use Disorders and HIV (Last updated July 10, 2019; last reviewed July 10, 2019)

Key Considerations and Recommendations

- Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care **(AII)**.
- The most commonly used substances among people with HIV include alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco.
- Health care providers should be nonjudgmental when addressing substance use with their patients **(AIII)**.
- Persons with HIV and SUDs should be screened for additional mental health disorders **(AII)**.
- Persons with HIV and SUDs should be offered evidenced-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment; see Table 13) as part of comprehensive HIV care in HIV clinical settings **(AI)**.
- Ongoing substance use is not a contraindication to antiretroviral therapy (ART) **(AI)**. Persons who use substances can achieve and maintain viral suppression with ART.
- Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors), the potential for drug-drug interactions, and the risk or severity of substance-associated toxicities (e.g., increased hepatotoxicity or an increased risk of overdose).
- Selection of ART regimens for individuals who practice unhealthy substance and alcohol use should take potential adherence barriers, comorbidities which could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug-drug interactions, and possible adverse events associated with the medications into account **(AII)**.
- ART regimens with once-daily dosing of single-tablet regimens, high barriers to resistance, low hepatotoxicity, and low potential for drug-drug interactions are preferred **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Background on Substance Use Disorders among People with HIV

Ending the HIV epidemic requires addressing substance use among people with HIV, which poses a barrier to optimal engagement in the HIV care continuum. Ongoing substance use may prevent an individual from being tested for HIV, initiating antiretroviral therapy (ART), or adhering to ART, and it may increase the frequency of behaviors that put a person at risk for HIV transmission. Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors, needle sharing, and injection of substances), the potential for drug-drug interactions, and the risk or severity of substance-related toxicities (e.g., increased hepatotoxicity and increased risk of overdose). In the United States, the death toll for drug overdose (70,237 deaths in 2017)[1] now far exceeds the death toll for HIV (15,807 deaths in 2016).[2] As the drug overdose epidemic continues to expand, health care providers need to have a basic understanding of how to screen for and treat substance use disorders in persons with HIV in clinical settings.[3]

Substance use exists on a continuum from episodic use to a substance use disorder (SUD) with its concomitant negative consequences. Research on alcohol consumption has defined a threshold at which consumption does not reach a diagnosis of a SUD, but where the level of consumption is nonetheless hazardous to the person. This level of consumption has been defined as "hazardous drinking." A comparable category does not exist for other substances. The prevalence of substance use and SUDs is higher among people with HIV than among the general public,[4] and polysubstance use is common. This section will focus on the most commonly used substances among people with HIV: alcohol, benzodiazepines, cannabinoids, club drugs,[5] opioids, stimulants (cocaine and methamphetamines), and tobacco.

Persons with HIV may use more than one substance and may not be ready to consider reducing the use of substances or seeking treatment for SUDs. Polysubstance use occurs for multiple reasons, including to

improve the euphoria associated with use (e.g., use of cocaine and heroin mixtures called "speedballs") and to reduce the adverse effects of a particular substance (e.g., the use of alcohol or benzodiazepines to reduce the anxiety caused by cocaine use).

Substance Use and Sexual Risk Taking

There is a growing body of literature describing the intersection of substance use and sexual risk taking ("chemsex"). While a precise definition of "chemsex" is lacking, and the various studies have investigated the use of many different substances, this research highlights the impact of substance use on sexual risk behaviors. In these settings, substances may be used to enhance sexual pleasure, decrease inhibitions related to particular sexual acts, and combat low self-esteem. In a retrospective study in a London sexual health clinic, individuals who disclosed substance use (463 of 1,734 patients) had higher odds of acquiring new HIV infection, bacterial sexually transmitted infections (STIs), and/or hepatitis C virus (HCV).[6] A much larger analysis using the European Men Who Have Sex with Men (MSM) Internet Survey, which collected data from 16,065 United Kingdom-based respondents, found that MSM who reported using methamphetamines or gamma-hydroxybutyrate (GHB) during the previous year were more likely to have gonorrhea infection than MSM who did not use these drugs, with odds ratios of 1.92 and 2.23, respectively.[7] These data emphasize the need to screen patients for substance use and STIs in clinical settings.

Screening for Substance Use Disorders

Screening for SUDs should be incorporated into the routine clinical care of all persons with HIV. The following questions can be used to screen for drug or alcohol use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had X or more drinks in a day?" (X is five for men and four for women).[8] Data are lacking on the appropriate threshold for alcohol use among transgender individuals, so until data clarifies the risks, providers should use the more conservative threshold of four drinks. Individuals with liver disease, including active HCV infection, should not consume alcohol. A positive response of at least one time on either screen should prompt additional screening with other short, yet effective screening tools (see the Screening and Assessment Tools Chart from the National Institute on Drug Abuse). These tools can identify substance use and guide decisions on appropriate treatment interventions. There is currently not enough data to determine how often patients should be screened for SUDs; however, given the potential negative impact that SUDs may have on persons with HIV, it is advisable to ask these questions during every clinical visit.

Health care providers should be nonjudgmental when discussing substance use with their patients. Patients who experience stigma or who feel judged may not trust the health care provider's recommendations, may avoid returning to see that provider again, and may consequently have poorer health outcomes.[9] Language is one way in which stigma is communicated, and words such as "addict" and "dirty urine" convey a negative connotation. The Office of National Drug Control Policy (ONDCP), the American Medical Association, the American Society of Addiction Medicine, the International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, non-stigmatizing language for substance use as described in the "Changing the Language of Addiction" report from ONDCP.

Co-Occurring Mental Illness

Many people who use substances have co-occurring mental health disorders, including a history of trauma that may drive and/or exacerbate their substance use. Conversely, ongoing use of substances can place individuals at risk of trauma, such as sexual assault and sexual exploitation, which may further exacerbate their substance use.[6,10] People with SUDs should undergo evaluation and treatment for concurrent mental health disorders using standardized screening instruments (e.g., the Patient Health Questionnaire-2 [PHQ-2] for depression).[11] Where applicable, clinicians should use available behavioral and pharmacological interventions to address mental health concerns, because recommending that patients stop their substance use without providing treatment for underlying mental health conditions has very limited efficacy.[11]

Several behavioral interventions have shown promise in randomized trials. Motivational interviewing, cognitive behavioral therapy, or a combination of the two have led to decreases in stimulant use, decreases in risky sexual behaviors, and improved adherence to ART.[12] Contingency management, a behavioral intervention that provides rewards for abstinence, has been shown to be effective in decreasing stimulant use among persons with HIV, but the sustained effects of this intervention are less clear.[13]

Selecting and Initiating an Antiretroviral Therapy Regimen

Ongoing substance use is not a contraindication to prescribing ART. Indeed, ART reduces the risk of HIV transmission to sexual and drug-using partners. These clinical, community, and individual benefits should encourage health care providers to initiate ART in people with HIV who use substances, and for those with SUDs.

When selecting ART regimens for individuals who use substances, clinicians should consider potential barriers to adherence (see Adherence to the Continuum of Care), co-morbidities that could impact care (e.g., advanced liver disease from alcohol or HCV), potential drug-drug interactions, and possible adverse events that are associated with the medications. Providers should discuss adherence with their patients during multiple, nonjudgmental evaluations. In general, the use of simplified ART regimens should be considered to aid ART adherence. Regimens for people with SUDs should be easy to take, such as a once-daily, single-tablet regimen,[14] and have a high barrier to resistance or a low risk of hepatotoxicity. Adherence counseling should highlight the benefits of ART use, irrespective of concurrent substance use. Additionally, a reduction in substance use may improve adherence to ART.[15]

Commonly Used Substances and Their Impact on HIV and Antiretroviral Therapy

Health care providers should have a basic understanding of evidence-based treatments for SUDs, including alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The sections below discuss the impact of these substances on persons with HIV and how these substances affect ART use.

Alcohol

Epidemiology

Alcohol consumption is common among persons with HIV. Recent estimates indicate that >50% of persons with HIV in the United States consume any amount of alcohol (with a range of 54% to 67%).[16,17] Among a sample of persons with HIV across seven university-based HIV clinics in the United States, 27% of people screened positive for unhealthy alcohol use as determined by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C).[17] Unhealthy alcohol use includes a spectrum of consumption, including risky or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[18]

Risk-Taking Behaviors, the HIV Care Continuum, and Comorbidities

Unhealthy alcohol use has been linked to HIV acquisition, as unhealthy alcohol use can increase the frequency of behaviors that put a person at risk for sexual transmission of HIV.[19-21] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts were all associated with condomless sex among persons with HIV.[20]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[22,23] Studies have demonstrated both temporal and dose-related relationships between alcohol use and adherence, where ART is more likely to be missed on a given drinking day and the day after drinking, with a stronger association on heavy (binge) drinking days.[24-26] The negative impact of unhealthy alcohol use on ART adherence is likely multifactorial and driven by the effects of intoxication, ART regimen complexity, and patient perceptions of adverse interactions between alcohol and ART drugs.[27-29] Studies have also demonstrated an association between unhealthy alcohol use

and the loss of durable viral suppression,[30,31] greater time spent with a viral load >1,500 copies/mL after ART initiation,[32] increased risk of viral rebound, lower retention in care,[33,34] and increased mortality.[35-37] Unhealthy alcohol use alone (hazardous or AUD) and in combination with other common comorbidities, including viral hepatitis coinfection, can hasten liver fibrosis progression in persons with HIV.[38,39] Finally, in general medical populations, unhealthy alcohol use complicates the management of diabetes mellitus, hypertension, mental health disorders, other substance use, and other chronic diseases and increases the risk for pneumonia, osteoporosis, a number of cancers (e.g., liver, head and neck, and breast cancers), and tuberculosis.

Management of Unhealthy Alcohol Use

On-going alcohol use is not a contraindication for a person to receive ART. However, treatment for unhealthy alcohol use may further improve HIV treatment outcomes. Behavioral treatments for unhealthy alcohol use among persons with HIV demonstrate a small but significant reduction in alcohol use[40] (see additional resources for alcohol management from the National Institute on Alcohol Abuse and Alcoholism and the American Public Health Association). Pharmacotherapy can also reduce alcohol use among persons with HIV. There are three Food and Drug Administration (FDA)-approved pharmacotherapies for AUD: naltrexone, disulfiram, and acamprosate (see Table 13).

Clinical trials have demonstrated the efficacy of naltrexone in reducing the number of heavy drinking days among those with HIV and among the general population. Naltrexone appears to be safe to use in persons with HIV,[41,42] and it is not associated with significant drug-drug interactions or irreversible hepatotoxicity. However, it is not recommended for individuals with decompensated liver disease and should be used with caution in individuals with elevated transaminase levels. Use of naltrexone in persons with HIV and AUD can improve HIV treatment outcomes. In a randomized placebo-controlled trial of 100 prisoners with HIV who met the criteria for AUD, individuals who were provided depot naltrexone upon release from prison were more likely to achieve viral suppression at 6 months than the placebo group (56.7% vs. 30.3%).[42]

Data on the use of disulfiram and acamprosate among persons with HIV are lacking. Notably, integrating treatment for AUD with treatment for HIV has been shown to increase the number of patients who receive alcohol treatment medication, counselling, and formal outpatient alcohol treatment services. Integrating these treatments may also improve the likelihood that a patient will achieve viral suppression on ART. A randomized controlled trial of 128 individuals with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veteran's Administration HIV clinics to treatment as usual. At end of treatment (24 weeks), integrated stepped care resulted in more participants receiving pharmacotherapy for AUD and participating in counseling. Though differences in alcohol use and viral suppression were not seen at 24 weeks, at 52 weeks integrated stepped care was significantly associated with an increased number of alcohol abstinent days, a decrease in the number of drinks per drinking day, and a decreased number of heavy drinking episodes. In addition, the patients in the stepped care group had increased odds of achieving viral suppression (odds ratio [OR] 5.58; 95% confidence interval [CI], 1.11–27.99).[43]

Liver cirrhosis, whether related to chronic heavy alcohol use, viral hepatitis, or nonalcoholic fatty liver disease, can result in altered metabolism of antiretroviral (ARV) drugs. For those who have hepatic impairment due to alcohol-related liver disease, ART dosing should follow the recommendations in Appendix B, Table 10, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

While specific epidemiologic data on the prevalence of benzodiazepine use among persons with HIV are limited, the use of benzodiazepines can impact both morbidity and mortality. Benzodiazepines cause anterograde amnesia, defined as difficulty recalling events after taking the medication. Individuals do not develop tolerance to this neurocognitive effect, and long-term use of benzodiazepines may result in impairment of neurocognitive functioning.[44]

Risk-Taking Behaviors and the HIV Care Continuum

People who inject drugs and who also use benzodiazepines engage in riskier behaviors than the people who inject drugs but who do not use benzodiazepines; these behaviors may include paying for sex, sharing injection equipment with more people, and performing more frequent injections.[45] A cohort of 2,802 people who injected drugs was followed from 1996 to 2013. During that time, benzodiazepines were the substances with the greatest association with mortality.[46] The long-term neurocognitive impact of benzodiazepines on ART adherence among persons with HIV is unclear, but prescribing a memory-impairing medication to persons with HIV who are prone to neurocognitive impairments from other causes increases the risk of poor ART adherence.[47] Benzodiazepines are also used illicitly to counteract the negative side effects of stimulants such as cocaine and methamphetamine.[48]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiologic dependence and life-threatening withdrawal in some patients. When feasible, individuals who chronically take benzodiazepines should be slowly tapered off the benzodiazepines under the supervision of an experienced clinician. Different benzodiazepines have different potencies (e.g., alprazolam is more potent than diazepam) and therefore require different tapers in terms of length and graduated decrease in dosage.

Benzodiazepine and Antiretroviral Drug Interactions

Several pharmacological interactions with ARV drugs have also been described. For example, some benzodiazepines are cytochrome P (CYP) 3A4 substrates; thus, when these benzodiazepines are used with a ritonavir-boosted or cobicistat-boosted ARV drug, their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See Drug-Drug Interactions for available data on benzodiazepine-related interactions.[49]

Cannabinoids

Epidemiology

Both medical and recreational cannabis (marijuana) use are prevalent among people with HIV.[50] Cannabis belongs to a class of compounds that activate cannabinoid receptors. This class, known as cannabinoids, also includes synthetic compounds such as K2. In recent years, cannabinoids have become more popular. In 2009, two cannabinoids were reported to the National Forensic Laboratory Information System. By 2015, 84 compounds had been reported.[51] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[52]

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Cannabis has not been shown to negatively impact adherence to ART or a patient's ability to achieve viral suppression. In one study, among 874 persons with HIV, daily cannabis use did not predict lower odds of ART use or achieving an undetectable HIV RNA level, except when combined with binge drinking.[53] Data from the Multicenter AIDS Cohort Study have supported the idea that marijuana use does not predict problems with adherence to ART or achieving viral suppression.[54] In some cases, however, cannabinoids have been listed as the cause of death in overdoses. While data are lacking among adults with HIV, the nationally representative 2015 Youth Risk Behavior Survey (which includes data from 15,624 adolescent students in grades 9 to 12) found that students who had ever used synthetic cannabinoids engaged in riskier activities, including sex, than students who only used marijuana.[55] While the available data suggest that the use of marijuana in not associated with decreased adherence to ART,[56] data are currently lacking on the impact of synthetic cannabinoids on ART adherence. Finally, with the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these products, which may increase the risk of opioid overdose.

Management of Cannabinoid Use

Due to the aforementioned concerns regarding cannabinoid use—particularly the variety of compounds and neuropsychiatric effects—persons with HIV should be discouraged from using cannabinoids until more data are available. There is no pharmacological treatment for cannabinoid use disorder; however, behavioral health treatment may be effective for some patients.[57-59]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects, or that are used to enhance sexual experiences.[5] The use of multiple club drugs or other drugs simultaneously is common. While these substances are used by many different persons with HIV, the majority of data comes from MSM with HIV. Use of club drugs in this population has been shown to negatively impact HIV treatment.[60] Club drugs include methylenedioxymethamphetamine (MDMA), GHB, ketamine, benzodiazepines (see the benzodiazepine section above), and other drugs that are used to enhance the sexual experience (e.g., mephedrone, inhaled nitrates [poppers], and phosphodiesterase-5 inhibitors [PDE5] for erectile dysfunction). Survey data from users of club drugs have also revealed that efavirenz is purchased by people without HIV for its intoxicating effects.[61]

Risk-Taking Behaviors and the HIV Care Continuum

Club drugs have disinhibitory effects. Using club drugs increases the likelihood that a person will engage in high-risk sexual practices, which can increase the risk of HIV transmission. In addition, these disinhibitory effects can lead to poor ART adherence.[49,60,62]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[63] There are no recommended pharmacotherapies at this time, and the most common strategy for treating patients who use club drugs is to employ the behavioral interventions that are used for other drug use disorders.

Club Drug and Antiretroviral Drug Interactions

MDMA, GHB, ketamine, and methamphetamine all have the potential to interact with ARV drugs because they are metabolized, at least in part, by the CYP450 system.[49,62] Overdoses secondary to interactions between the club drugs (i.e., MDMA or GHB) and protease inhibitor-based ART have been reported.[49] For instance, using PDE5 or ketamine concurrently with potent CYP3A4 inhibitors such as ritonavir or cobicistat can lead to potentiation of the effects of these substances.[60]

Cocaine

See the discussion in the section on stimulants below.

Opioids

Epidemiology

Opioids remain a significant concern for persons with HIV, both for the acquisition of HIV (as recently demonstrated in Scott County, Indiana[64]) and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[65] The appropriate use of opioids while caring for people with HIV and chronic pain is an important component of combating the opioid epidemic, but this subject is beyond the scope of this section. Please refer to additional resources, such as those from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America.[66] To combat the opioid overdose epidemic, health care providers should prescribe naloxone for opioid overdose prevention for all patients who are using opioids beyond the short-term treatment of acute pain.[3]

Risk-Taking Behaviors and the HIV Care Continuum

Many people who use opioids start by using opioid tablets (e.g., oxycodone) that are ingested orally or crushed and sniffed. Once tolerance develops, some individuals move from sniffing the crushed tablets to injecting heroin purchased on the streets. This transition from sniffing to injecting dramatically increases the risk of HIV and HCV infection.

Low-cost heroin is often a mix of heroin and higher potency synthetic opioids, such as fentanyl.[65] Methamphetamines and cocaine have also been combined with fentanyl, but at a lower rate than heroin.[67,68] With the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these as well. In all instances where fentanyl or other high-potency opioids are added to other drugs, the risk of overdose increases.

While treatment for an opioid use disorder can improve HIV treatment outcomes, it is not a prerequisite for treating HIV, as some patients are able to successfully adhere to ART despite ongoing opioid use. Although ART coverage among people with HIV who injected drugs increased from 58% to 71% between 2009 and 2015, additional work is needed to improve ART coverage in this population.[69] Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people who injected drugs were less likely to be retained in care; however, this gap in retention had closed by 2012, and people who injected drugs and noninjectors had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort.[70]

Management of Opioid Use

There are three FDA-approved medications for the treatment of opioid use disorder that can help decrease or eliminate opioid use, reduce the risks of morbidity and mortality that are associated with opioid use, and improve HIV treatment success. These medications, collectively termed medication-assisted treatment (MAT), include buprenorphine, methadone, and naltrexone (see Table 13). Buprenorphine and methadone are opioid agonists (the use of these drugs is termed opioid agonist therapy [OAT]), while naltrexone is an opioid-antagonist or "blocker." Both buprenorphine and naltrexone can be prescribed in the setting of routine HIV clinical care.[71] Prescribing buprenorphine requires specific training and licensure (known as an X-waiver; see the Substance Abuse and Mental Health Services Administration [SAMHSA] website for more information). Methadone must be prescribed through a licensed opioid treatment program (OTP). An OTP directory can also be found on the SAMHSA website.

Use of buprenorphine or methadone can lead to reductions in risky behaviors associated with HIV transmission, psychosocial and medical morbidity related to opioid use disorder, and criminal behaviors. People who are receiving treatment for opioid use are already engaging with the health care system; therefore, they are more likely to initiate treatment for HIV and to be adherent to their ART regimens. Both buprenorphine and methadone are cost-effective interventions at the societal level.[72] Methadone has better retention in SUD treatment than either buprenorphine or naltrexone, and it should be considered for individuals who do not achieve successful outcomes with buprenorphine or naltrexone.[73] Buprenorphine has a lower risk of overdose than methadone. In addition, it can be prescribed in primary care offices. Patients who are taking buprenorphine have significantly better retention in treatment than those who are taking daily oral naltrexone.[74] While several randomized, controlled clinical trials have demonstrated efficacy for naltrexone when treating opioid use disorder, subsequent study results have been disappointing; one meta-analysis revealed that oral naltrexone was equivalent to placebo.[75] To address the adherence challenges with naltrexone, a depot formulation was created for monthly administration. This preparation has the potential to improve adherence; however, studies that compare opioid agonists such as buprenorphine and methadone to depot naltrexone as treatments for opioid use disorder have not been conducted. In a randomized, placebo-controlled trial in persons with both HIV and opioid use disorder, participants who received at least three doses of depot naltrexone prior to discharge from prison achieved longer periods of continuous abstinence

after transitioning from prison to the community than those who received either placebo or two or less doses of depot naltrexone.[42] On the basis of these data, methadone or buprenorphine are generally used as first-line agents for the treatment of opioid use disorder. Depot naltrexone is used as an alternative treatment for people who have recently been released from correctional facilities when other options are not available.

Important pharmacokinetic interactions between these medications (particularly methadone) and certain ARV drugs are listed in Drug-Drug Interactions.

Stimulants

Epidemiology

Cocaine and methamphetamine are powerful stimulants that have been associated with multiple detrimental effects to people with HIV, including accelerated disease progression, poor ART adherence, and lack of viral suppression. Cocaine powder is snorted or injected, while the free-base form (crack) is smoked. Methamphetamines can be taken orally or rectally, injected, or smoked. Cocaine and methamphetamine are commonly used with other substances, including alcohol. Individuals who use stimulants experience a sense of euphoria and may have heightened sexual desire and arousal. This can lead to disinhibited sexual behaviors, increasing the risk of HIV transmission.

The prevalence of stimulant use among people with HIV has been estimated to be 5% to 15% across multiple studies.[76-78] Methamphetamine use is more common among MSM,[79] and increased rates of cocaine use have been observed among ethnic and racial minorities and persons with a history of incarceration.[80]

Risk-Taking Behaviors and the HIV Care Continuum

There are multiple negative health consequences of stimulant use among persons with HIV, including rapid development of dependence and adverse effects on multiple organ systems, particularly the central nervous and cardiovascular systems. Stimulant use is associated with neurocognitive impairment,[81] delirium, seizures, hemorrhagic strokes, and mental health disturbances, including anxiety, psychosis, and paranoia.

Stimulant use may independently lead to HIV disease progression even among persons who are taking ART and who have achieved viral suppression. Research to identify the cellular mechanisms responsible for this is ongoing, but increased viral replication, direct effects on the immune system that lead to declines in CD4 T lymphocyte cell count, enhanced immune activation, and disruption of the blood brain barrier that facilitates HIV entry into the brain have been implicated.[82-85] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence, retention in care, and viral suppression. Lack of viral suppression, combined with the increased likelihood of risky sexual behaviors that occurs under the influence of stimulants, poses a threat to the HIV treatment as prevention paradigm.[86]

Non-opioid substances, including methamphetamines and cocaine, are sometimes combined with fentanyl, which increases the risk of overdose.[67,68]

Management of Stimulant Use

Several pharmacologic and behavioral interventions for stimulant dependence have been investigated, and some trials have included people with HIV. The results of pharmacologic interventions have generally been disappointing. There is no FDA-approved pharmacotherapy for cocaine use disorder at this time, despite research on multiple drug classes, including antidepressants, antipsychotics, anticonvulsants, and dopaminergic medications (e.g., disulfiram).[87,88] Among persons with HIV who use crack and opioids, MAT for opioid use disorder may improve ART adherence and viral suppression.[89,90] There is limited evidence that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone)[91] can reduce methamphetamine use or cravings, yet there is no recommended pharmacotherapy to treat stimulant use disorder in persons with HIV.

Several behavioral interventions have shown promise in randomized trials. People with HIV who received

motivational interviewing sessions, cognitive behavioral therapy, or a combination of the two decreased their stimulant use and improved their adherence to ART, and they were less likely to engage in risky sexual behaviors.[12] Contingency management has been shown to be effective in decreasing stimulant use among persons with HIV, but the sustained effects on the reduction of stimulant use and improvements in ART adherence are less clear.[13,77,92] Technology-based interventions, such as text messaging, may have a role in supporting ART adherence and decreasing methamphetamine use among persons with HIV, but further research is needed.[93] Persons with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[12]

Despite the challenges discussed above, persons with HIV who use stimulants can achieve viral suppression with ART[94] and should be prescribed ART even if stimulant use is ongoing.

Tobacco

Epidemiology

The prevalence of tobacco smoking among persons with HIV in the United States is approximately twice that of the general population (33.6% vs. 16.8%). Prevalence is even higher among specific subgroups, including those who use alcohol and/or other drugs, those who have concurrent mental health disorders, and those of a lower socioeconomic status. While smoking rates are declining overall in the United States, persons with HIV are less likely to quit smoking than people in the general population.[95]

Associated Risks of Tobacco Use and HIV Infection

With respect to substance use and HIV, tobacco smoking is the biggest threat to health-related gains achieved through ART. Among individuals with viral suppression on ART, more years of life may be lost from continued smoking than from HIV infection itself.[96,97] Tobacco smoking among persons with HIV is associated with an increased risk of numerous health conditions, including lung cancer and other smoking-related cancers, cardiovascular disease, and pulmonary disease. In a sample of 17,995 persons with HIV on ART in Europe and North America, individuals who smoked had nearly twice the mortality of those who did not (mortality rate ratio 1.94; 95% CI, 1.56–2.41) with significant mortality attributed to cardiovascular disease and non-AIDS related malignancy.[96] Importantly, tobacco cessation reduces the incidence of cardiovascular disease and smoking-related cancers (though definitive data on lung cancer are not available) and improves quality of life.[98-100]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[101-103] cessation strategies when treating patients with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and the U.S. Preventive Services Task Force). These include (but are not limited to) advising the patient to quit smoking, using the five A's, employing motivational interviewing, and referring the patient to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion, and varenicline) have few clinically significant interactions with ARV drugs and can lead to enormous reductions in morbidity and mortality if the person is able to stop smoking. Nicotine replacement is efficacious;[104] however, bupropion doubles rates of smoking cessation compared with nicotine replacement therapy.[105] Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[105,106] Clinical trials among persons with HIV have found varenicline to be both effective and safe.[101,103] In a recent randomized controlled trial among 179 individuals with HIV who were randomized to receive 12 weeks of behavioral counseling and either varenicline or placebo, varenicline use led to an increase in the percentage of participants who achieved a 7-day abstinence period at 12 weeks (28.1% vs. 12.1%, OR 4.5; 95% CI, 1.83–11.2) and produced higher continuous abstinence between weeks 9 and 12 (23.6% vs. 10%, OR 4.65; 95% CI, 1.71–12.67) compared to placebo.[103] While significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among persons with HIV. Varenicline should be used

in combination with relapse prevention strategies and other measures for long-term tobacco cessation.

Table 13. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction with ARV Drugs	Comments
Alcohol Use Disorder			
Acamprosate	666 mg PO three times a day *or* 333 mg PO three times a day for patients with CrCl 30–50 mL/min	No significant interaction with ARV drugs expected.	**Contraindicated** in patients with CrCl <30 mL/min.
Disulfiram	250 mg PO once daily	Use with caution when prescribing an ARV oral solution that contains ethanol and/or propylene glycol (e.g., FPV, LPV/r, RTV).	Counsel patients regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for alcohol use disorder.
Opioid Use Disorder			
Buprenorphine	Individualize buprenorphine dosing based on a patient's opioid use. The dose range is 4–24 mg sublingually. Dosing is once daily or twice daily.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	Buprenorphine has 90% first pass hepatic metabolism. Verify that the patient is using the appropriate technique for sublingual administration before adjusting the dose, as improper administration will result in poor absorption and low drug levels.
Methadone	Individualize dose. Patients who receive higher doses (>100 mg) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	QTc prolongation is a concern at higher doses. Methadone can only be prescribed for OUD by a licensed OTP.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Longer time of continuous abstinence in those who received depot formulation naltrexone compared to placebo after transition from prison to community.
Nicotine Use Disorder			
Nicotine Replacement Therapy	There are a wide variety of FDA-approved nicotine replacement products. All formulations are effective.	No significant interaction with ARV drugs expected.	Work with the patient to identify the route of delivery that the patient will use and find most helpful.
Bupropion	Start at 150 mg PO daily for three days, then increase to either 150 mg twice daily or 300 mg once daily (only use formulations that are approved for once daily dosing).	Concentration may be reduced when used with ARV drugs that are CYP2D6 inducers. See Drug-Drug Interactions for further recommendations.	Tobacco quit date should ideally be 1 week after starting therapy.
Varenicline	Titrate dose based on tolerability until desired effect is achieved. The goal is to reach a dose of 1 mg PO twice daily. Requires dose adjustment in patients with CrCl <30 mL/min.	No significant interaction with ARV drugs expected.	Tobacco quit date should ideally be 1 week after starting therapy.

Key: ARV = antiretroviral; CrCl = creatinine clearance; CYP = cytochrome P; FDA = Food and Drug Administration; FPV = fosamprenavir; LPV/r = lopinavir/ritonavir; OUD = opioid use disorder; OTP = opioid treatment program; PO = orally; RTV = ritonavir; SR = sustained release

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Transgender People with HIV (Last updated December 18, 2019; last reviewed December 18, 2019)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all transgender people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners **(AI)**.
• HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and to maximize the likelihood of achieving sustained viral suppression **(AII)**.
• Prior to ART initiation, a pregnancy test should be performed for transgender individuals of childbearing potential **(AIII)**.
• Some antiretroviral drugs may have pharmacokinetic interactions with gender-affirming hormone therapy. Clinical effects and hormone levels should be routinely monitored with appropriate titrations of estradiol, testosterone, or androgen blockers, as needed **(AIII)**.
• Gender-affirming hormone therapies are associated with hyperlipidemia, elevated cardiovascular risk, and osteopenia; therefore, clinicians should choose an ART regimen that will not increase the risk of these adverse effects **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Because transgender and nonbinary people bear a disproportionate burden of HIV, it is important for HIV care providers to be knowledgeable about the specific HIV care needs of these individuals.

Terminology

Transgender people are broadly defined as those whose gender identity differs from their assigned sex at birth.[1,2] The terminology used to define transgender identities continues to evolve over time and across geographical and cultural contexts.[3] The terms cisgender, cis-man, and cis-woman are used to describe persons who identify with their assigned sex at birth. The terms used to describe women who were assigned male at birth include transgender women, trans women, transfeminine individuals, and women of transgender experience. The terms for men who were assigned female at birth include transgender men, trans men, transmasculine individuals, and men of transgender experience. Some individuals identify outside the gender binary of man or woman, using words such as gender nonbinary, genderqueer, and gender nonconforming to describe themselves. Other individuals may not have a fixed sense of their gender and may move back and forth among different gender identities; these individuals are described as gender fluid. Agender persons do not identify with having any gender and can use other terms such as null-gender or neutrois.

Gender affirmation describes processes whereby a person receives social recognition, value, and support for their gender identity and expression.[4] Gender affirmation is often described across several dimensions, including social (e.g., social support and acceptance, use of pronouns, names, or clothing that align with their gender identity), medical (e.g., use of hormones or surgery), legal (e.g., legal name change or changing gender markers on identity documents), and psychological (e.g., the degree of self-acceptance and comfort with their gender identity).[5] Medical gender affirmation has been shown to improve mental health outcomes and measures of well-being in transgender individuals.[6,7]

Epidemiology

National surveys indicate that 1.4 million adults in the United States aged 18 years and older identify as transgender, representing 0.6% of the adult population.[8] It is estimated that almost 2% of high school students identify as transgender.[9,10] National, population-based estimates of the numbers of gender nonbinary people in the United States are not yet available; however, 31% of the 27,715 people who completed the 2015 U.S. Transgender Survey (USTS) identified as gender nonbinary.[11] Meta-regression modeling suggests that the number of people who are willing to report that they are transgender and/or gender nonbinary is likely to increase in the future.[12]

The most recent estimate of HIV prevalence among transgender people is 14% among transgender women and 2% among transgender men.[13] The highest prevalence is among black (44%) and Hispanic/Latino (26%) transgender women.[13] Not enough data were available to estimate HIV prevalence by race/ethnicity among transgender men. Data on HIV prevalence among nonbinary individuals is scant. Of the nonbinary individuals who completed the 2015 USTS, 0.4% self-reported having HIV, including 1% of participants who were assigned male at birth and 0.2% of participants who were assigned female at birth.[11]

In the first national-level analysis of transgender people with HIV, the National HIV Surveillance system identified 2,351 transgender people with newly diagnosed HIV infection from 2009 to 2014. Eighty-four percent of these individuals were transgender women, 15% were transgender men, and 0.7% reported other gender identities.[14] More than one-half of both transgender women (51%) and men (58%) with newly diagnosed HIV were black/African American. Most of these individuals were aged 25 years to 34 years (35%) or 20 years to 24 years (26%). Almost one-half of transgender people with newly diagnosed HIV resided in the South (44%), and 18% had AIDS at the time of diagnosis.

In 2017, the Ryan White HIV/AIDS Program provided services for 8,811 transgender people, representing 1.8% of Ryan White clients.[15] Of these transgender clients, 7,837 (89%) were transgender women, 853 (10%) were transgender men, and 121 (1%) were transgender with current gender unknown. The majority were black and/or African American (5,081 individuals [57.6%]) or Hispanic/Latino (2,619 individuals [29.7%]).

HIV Care Continuum

Some studies have reported that transgender women living with HIV are less likely than cisgender men to receive antiretroviral therapy (ART), be adherent to ART, and achieve viral suppression.[16-21] Transgender people may experience numerous barriers to successful engagement along the HIV care continuum.[11,22] For example, compared with Ryan White clients overall, transgender clients were significantly less likely to have stable housing (77% vs. 87%), live above the federal poverty level (24% vs. 37%), and be virally suppressed (81% vs. 86%).[15] Experiences of violence, discrimination, and other trauma[11] are common among transgender people and have been associated with ART failure.[23]

Barriers to HIV Care and Treatment

Transgender people may avoid the health care system due to stigma and past negative experiences (e.g., being called the wrong name or pronoun, being verbally harassed, asked invasive questions about being transgender, or having to educate their providers about transgender people).[11,13,14,24-26]

For many transgender people, gender-affirming therapy (e.g., feminizing hormones) is a greater priority than HIV treatment and care.[27,28]

Concerns about adverse interactions between antiretroviral (ARV) drugs and gender-affirming hormone therapy are common among transgender people.[27] One study found that 40% of transgender women with HIV did not take their ARV drugs as directed due to concerns about drug-drug interactions, yet less than half had discussed this concern with their providers.[29]

Facilitating HIV Care Engagement

Gender Affirmation

Individuals are more likely to engage in HIV care when gender affirmation needs are met.[4,25] A national study of transgender people with HIV found that participants who work with HIV care providers who affirm their gender (e.g., providers who use their chosen name and pronoun) were more likely to be virally suppressed.[28] Adherence to hormone therapy correlates with adherence to ART.[30,31] However, making access to hormone therapy contingent upon ART adherence is associated with lower likelihood of viral suppression.[28]

Integration of HIV Care with Gender Care

According to research with transgender youth[25] and adults,[27] integrating HIV care with gender care facilitates

treatment and is associated with higher rates of viral suppression. In addition to minimizing the number of provider visits and potentially stressful clinical interactions, care integration makes it easier to discuss concerns about drug-drug interactions between HIV treatment and gender-affirming medications. In instances where integrated care is not feasible, the ART prescriber should refer the patient to an appropriate hormone therapy prescriber. Collaboration between these two care providers may enhance the quality of care.

Peer Navigation

Peer navigation has been found to improve the likelihood of durable viral suppression among key populations, including among transgender women.[32] Research with youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.[25]

Gender-Affirming Clinical Settings

Providing HIV services within gender-affirming environments should be a priority. Concrete steps that clinicians can take include ensuring that registration forms and electronic medical records are inclusive of transgender and gender nonbinary identities, preferably using a two-step method that records both gender and sex assigned at birth.[33] Individuals should be asked for their chosen name and pronouns, and these should be used consistently when speaking to or about the person, regardless of legal name. Clinicians and staff should avail themselves of resource lists, brochures, and other materials that meet the specific needs of transgender people with HIV.

Integrating hormone therapy with HIV services is the recommended practice; this requires HIV providers to become knowledgeable about hormone therapy and other aspects of gender-affirming services. When integration of HIV and transgender services is not possible, patients should be referred to clinicians who are knowledgeable in the field of transgender medicine. Both the World Professional Association for Transgender Health (WPATH) and GLMA: Health Professionals Advancing LGBTQ Equality (previously known as the Gay & Lesbian Medical Association) have provider directories that list endocrinologists, primary care providers, and psychiatrists with expertise working with transgender populations.

Pharmacological Considerations

Hormone Therapy

Hormone therapy is an important aspect of gender-affirming care for many transgender individuals. Hormones facilitate the acquisition of the secondary sex characteristics that are associated with the affirmed gender. Several guidelines for hormonal treatment of transgender people have been published, including guidelines from the Endocrine Society[34] and WPATH.[35] Clinical outcomes, potential adverse effects, the patient's treatment goals, and the patient's current hormone levels should be taken into account when determining the appropriate doses of hormone and androgen blockers. A clinician should be aware of the typical doses and routes of administration for all of the hormones and androgen blockers that a patient is taking, whether these medications are prescribed or not. All additional interventions (such as gonadectomy) should be documented. These interventions could potentially increase the risk of ART-related adverse effects on cardiovascular and bone health.

Feminizing regimens that are used by transgender women and others who were assigned male at birth usually include estrogens and androgen blockers. Feminizing regimens result in breast growth, redistribution of body fat, softening of the skin, and a decrease in muscle mass.[32] These regimens do not reduce facial (beard) hair or change the voice. In the United States, oral, parenteral, or transdermal preparations of 17-beta estradiol, or, less often, conjugated estrogens, are the mainstay of gender-affirming medical care for transgender women. Spironolactone, a mineralocorticoid receptor antagonist with anti-androgen properties, is usually used for androgen blockade; alternatives include 5-alpha reductase inhibitors that decrease the production of dihydrotestosterone (e.g., finasteride or dutasteride) or gonadotropin-releasing hormone agonists (e.g., goserelin acetate and leuprolide acetate). Cyproterone acetate is a steroidal anti-androgen that is frequently used outside of the United States. Patients may request progesterone to assist with breast growth; however, this has not been proven to be effective.[33] When using feminizing regimens, the goal is to suppress the testosterone level to <50 ng/dL and reach a serum estradiol level in the physiologic cisgender female range of 100 pg/mL to 200 pg/mL.[34]

Masculinizing regimens for transgender men and others who were assigned female at birth involve parenteral or transdermal testosterone preparations. These regimens are designed to stimulate the growth of facial and body hair, increase muscle mass, and deepen the voice; use of these regimens also results in clitoral enlargement, vaginal atrophy, and amenorrhea.[34] When using masculinizing therapy, the testosterone levels should be kept in the usual cisgender male range of 400 ng/dL to 700 ng/dL.[34]

Hormones and Antiretroviral Therapy

Studies that have examined interactions between exogenous estrogens and ART have predominantly focused on combined oral contraceptive use in cisgender women.[36] The data from these studies have been used to make predictions about the direction and extent of drug-drug interactions (Table 14). However, there are known differences between the pharmacologic characteristics of ethinyl estradiol, which is used in contraceptives, and 17-beta estradiol, which is used for gender affirmation. These differences may influence the accuracy of the predictions about the interactions between feminizing hormonal regimens and ART.

Table 14. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with the Least Potential to Impact GAHT Drugs	All NRTIs **Entry Inhibitors:** • IBA • MVC • T-20 **Unboosted INSTIs:** • BIC • DTG • RAL **NNRTIs:** • RPV • DOR	None	No dose adjustments necessary. Titrate dose based on desired clinical effects and hormone concentrations.
ARV Drugs that may Increase Concentrations of Some GAHT Drugs	EVG/c All boosted PIs	Dutasteride Finasteride Testosterone	Monitor patient for associated adverse effects; decrease the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs that may Decrease Concentrations of GAHT Drugs	PI/r **NNRTIs:** • EFV • ETR • NVP	Estradiol	Increase the dose of estradiol as needed to achieve the desired clinical effects and hormone concentrations.
	NNRTIs: • EFV • ETR • NVP	Dutasteride Finasteride Testosterone	Increase the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs with an Unclear Effect on GAHT Drugs	EVG/c PI/c	Estradiol	There is the potential for increased or decreased estradiol concentrations. Adjust the dose of estradiol to achieve the desired clinical effects and hormone concentrations.

Note: See Tables 21a, 21b, 21c, 21d, and 21e for additional information regarding drug-drug interactions between ARV drugs and gender-affirming medications.

Key: ARV = antiretroviral; BIC = bictegravir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GAHT = gender-affirming hormone therapy; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; T-20 = enfuvirtide

Other Hormonal Therapy Considerations

Bone Health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone removal of their gonads. Studies investigating bone mineral density changes in transgender women have shown inconsistent results, with the use of estrogens being associated with both elevations and declines in bone mineral density.[37-39] In one study, transgender women had high rates of osteopenia even before initiating hormones, possibly due to low levels of physical activity and low vitamin D levels.[37] Transgender men who are receiving testosterone appear to maintain adequate bone mineral density.[40] The risk for osteoporosis increases after gonadectomy for both transgender men and transgender women, especially if hormone regimens are stopped. Consequently, clinicians should consider early screening in this setting.

When using the FRAX® tool, which requires a sex designation, expert consensus is that assigned birth sex should be used, since transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass.[41] Transgender people with HIV should be screened for osteoporosis using dual-energy X-ray absorptiometry by age 50, in accordance with current primary care recommendations.[42]

Since the use of tenofovir disoproxil fumarate (TDF) has been associated with reductions in bone mineral density in people with HIV, TDF should be used with caution in transgender people with risk factors for osteoporosis or in those with established osteoporosis.

Interpretation of Laboratory Values

Interpretation of laboratory results requires special attention when reference ranges vary by sex. The sex listed on laboratory requisition forms typically corresponds with the gender listed on the patient's insurance forms and may not reflect the patient's current anatomical or hormonal configuration. Normal values have not been established for transgender individuals who are receiving gender-affirming hormonal or surgical interventions. Interpretation of laboratory results is dependent on the patient's physiology and the specific test being performed. Feldman et al.[43] recommend the following:

- For transgender people who are not taking hormones and have not had gonadectomy, use the sex assigned at birth.
- For transgender people who have undergone gonadectomy and have been stable on hormone therapy, use their affirmed gender.
- For transgender people who retain natal gonads and who may have been on hormone therapy for shorter periods of time, some laboratory tests may require the use of male reference ranges, while others may require the use of female reference ranges.
- Guidelines from the Center of Excellence for Transgender Health[1] recommend using the limits of normal described in the table below.

Limits of Normal When Interpreting Selected Laboratory Results in Transgender Adults

Laboratory Measures	Transgender Women on Gender-Affirming Hormones		Transgender Men on Gender-Affirming Hormones	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Alkaline Phosphatase	Not defined	Male value	Not defined	Male value
Creatinine	Not defined	Male value	Not defined	Male value
Hemoglobin/Hematocrit	Female value	Male value	Male value[a]	Male value

[a] If the patient is menstruating regularly, consider using the female lower limit of normal.

Providers are encouraged to consult with their local laboratories to obtain hormone level reference ranges for both male and female norms, and then apply the correct range when interpreting results based on the current hormonal sex, rather than the sex on the laboratory form.[1] Reference intervals for transgender people have not been established; therefore, hormone status and clinical judgment must be used to assess abnormal laboratory values.[44]

Renal Concerns

Gender-affirming hormones can affect estimates of glomerular filtration rates (eGFR) that rely on serum creatinine due to changes in muscle mass. In one study, transgender men on testosterone had a mean increase in levels of serum creatinine from 0.73 ± 0.03 mg/dL to 0.87 ± 0.04 mg/dL after 3 months to 6 months of treatment. Transgender women on estrogen had a decrease in mean serum creatinine levels from 0.90 ± 0.03 mg/dL to 0.85 ± 0.03 mg/dL.[45] Creatinine-based eGFR calculations may therefore overestimate GFR in transgender women on hormones or underestimate GFR in transgender men on hormones. Therefore, using cystatin C-based eGFR calculations may be preferred for patients with marginal renal function.

Cardiovascular Disease Risk

Transgender individuals may have elevated cardiovascular disease (CVD) risk, due to both traditional risk factors and the risk factors associated with hormone use. Rates of tobacco use are higher among transgender people than in the general population,[46] and transgender women have a higher risk of venous thromboembolism and ischemic stroke, primarily associated with duration of estrogen use.[47] Transgender women on estrogens may show an increase in serum levels of triglycerides and high-density lipoproteins (HDL) and a decrease in levels of low-density lipoproteins (LDL).[48] Exogenous testosterone has been associated with increased levels of LDL and decreased levels of HDL among transgender men.[48] Providers should take CVD risk into consideration when selecting ART regimens and gender-affirming hormone therapy regimens.

Assessment of cardiac risk among transgender people with HIV can be complicated by hormone-induced changes in lipid levels as well as sex-specific variations in levels of homocysteine and high sensitivity C-reactive protein.[49] American Heart Association guidelines recommend using sex-specific calculators to determine cardiovascular risk and guide interventions,[50] and they provide no guidance for transgender people whose assigned sex at birth may differ from their hormonal and/or anatomical sex. The Center of Excellence for Transgender Health recommends that providers use the risk calculator for the sex at birth, affirmed gender, or an average of the two depending on the age at which the patient began using hormones and the total amount of time that a patient has been on hormone therapy.[1]

For transgender people with an elevated CVD risk or a history of CVD events, ARV drugs that are associated with CVD should be avoided whenever possible. See Table 17 for a list of ARV drugs that are associated with an increased risk of CVD. See Table 18 for alternative ARV agents to use in individuals with CVD. In transgender women who have an elevated risk for CVD or who have experienced a CVD event, transdermal estradiol may be the safest option for hormone therapy, as it carries a lower risk of thromboembolism than other routes of administration.[51]

Pregnancy Potential

Important information on contraception, drug-drug interactions between ARV drugs and hormone therapy drugs, and pregnancy is provided in Women with HIV. Much of this information also applies to transgender and nonbinary individuals. Below are specific ART considerations for transgender and nonbinary people of childbearing potential. Clinicians who care for pregnant patients should also consult the current Perinatal Guidelines for a more in-depth discussion and guidance on managing these patients.

Some transgender individuals use exogenous hormones and/or undergo gonadectomy for gender affirmation. Understanding exactly what interventions someone has undergone and the timeline for these interventions will clarify the patient's potential for pregnancy. Transgender individuals without a uterus (by birth or by

hysterectomy) do not have pregnancy potential. Ovulation may continue in the presence of hormone therapy in transgender people with a uterus and ovaries, and these individuals may retain their fertility.[1] Gender-affirming surgeries do not impair fertility unless the uterus, ovaries, and vagina are removed.[52,53]

All transgender people who have a uterus and ovaries and engage in sexual activity that could result in pregnancy should receive a pregnancy test prior to initiating ART **(AIII)**. Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects in infants born to those who were receiving dolutegravir at the time of conception; however, the risk of these defects is still low. Before initiating an integrase strand transfer inhibitor-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen. All ART-naive persons who are pregnant should be started on ART for their health and to prevent transmission of HIV to the fetus. They should be counseled about ARV drug use during pregnancy, and clinicians should consult the Perinatal Guidelines when designing a regimen **(AIII)**.

Testosterone Exposure in Transgender Persons with Ovaries

Testosterone alone is not a reliable form of contraception, and pregnancies have been reported in transgender men following prolonged testosterone treatment. Testosterone is a teratogen, and it is contraindicated in pregnancy. Clinicians should assess the reproductive desires and fertility potential of their transgender patients and provide accurate information on contraceptive and reproductive options.[54]

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Women with HIV (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- Antiretroviral therapy (ART) is recommended for all persons living with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners without HIV **(AI)**.
- When prescribing antiretroviral (ARV) drugs, clinicians should take into account that some ARV drugs have significant pharmacokinetic (PK) interactions with hormonal contraceptives; an alternative or additional effective contraceptive method is recommended to prevent unplanned pregnancy **(AIII)**. Switching to an ARV drug that does not have interactions with hormonal contraceptives may also be considered **(BIII)**.
- A pregnancy test should be performed for those of childbearing potential prior to initiation of ART **(AIII)**.
- Preliminary data suggest there may be an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving dolutegravir (DTG) at the time of conception. Updated results have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower (0.3%) than reported in the preliminary data, but still higher than in infants born to women who received ART that did not include DTG (0.1%).
- Providers should discuss the potential risks and benefits of using DTG with individuals of childbearing potential and provide appropriate counseling so that individuals can make informed decisions.
- Before initiating an integrase strand transfer inhibitor-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.
- In a patient with multidrug-resistant HIV who has no alternatives to DTG, the decision of whether to use DTG should be made after carefully considering the risk of NTDs in the infant if pregnancy occurs while a patient is taking DTG, and the risks of persistent viremia in the patient and potential HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.
- During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy to reduce the risk of transmission to the fetus and newborn **(AI)**.
- When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and PK data on use during pregnancy for each agent. The risks and benefits of ARV use during pregnancy should be discussed with all individuals of childbearing potential **(AIII)** and clinicians should consult the most current Perinatal Guidelines when designing a regimen **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

This section focuses on some unique clinical and therapeutic issues to consider and basic principles to follow when caring for cisgender women living with HIV. Cisgender women are defined as women who were assigned female at birth and who identify themselves as women. Some topics discussed in this section, such as contraception, drug-drug interactions between antiretroviral (ARV) drugs and hormonal therapy, and pregnancy, also apply to transgender men (men assigned female at birth), and individuals assigned female at birth who identify as nonbinary (gender identities that are not exclusively feminine or masculine) or gender fluid (gender identity is not fixed). See Transgender People with HIV for more information on the specific HIV care needs of these individuals. Clinicians who care for pregnant patients should consult the current Perinatal Guidelines for a more in-depth discussion on treating pregnant patients and guidance on managing these patients.

Sex Difference Considerations in Antiretroviral Therapy

In general, studies to date have not shown sex differences in virologic responses to antiretroviral therapy (ART).[1-4] However, there are limited data showing that pharmacokinetics (PKs) for some ARV drugs may differ between men and women, possibly because of variations in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P 450 activity, drug transporter function, and excretion activity.[5-7]

Adverse Effects

Several studies with older ARV drugs have suggested that sex may influence the frequency, presentation, and severity of some ARV-related adverse events. Most notably, women are more likely to develop severe symptomatic hepatotoxicity with nevirapine (NVP) use[8,9] and are more likely to develop symptomatic lactic acidosis with prolonged use of older nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV), stavudine, and didanosine.[10] These agents are no longer recommended for use in people with HIV in the United States; although ZDV is still administered intravenously (IV) to some patients during delivery, it is not generally recommended for long-term use.

Some studies have investigated how metabolic complications that are associated with the use of ARV drugs differ between women and men. At 96 weeks after initiation of ART, women with HIV were less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than men with HIV.[11,12] Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.[13-16] ART regimens that contain tenofovir disoproxil fumarate (TDF), ritonavir-boosted protease inhibitors (PI/r), or both are associated with a significantly greater loss of BMD than regimens that contain other NRTIs and raltegravir (RAL).[17-20] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide may be considered as alternatives to TDF for patients who are at risk of osteopenia or osteoporosis. Recommendations for the management of bone disease in people with HIV have been published.[21]

Adults and Adolescents with HIV Who Are of Childbearing Potential

All adults and adolescents with HIV who are of childbearing potential should be offered comprehensive reproductive and sexual health counseling and care as part of routine primary medical care. Topics for discussion should include safe sex practices, reproductive desires and options for conception, the HIV status of sexual partner(s), and the use of effective contraception to prevent unplanned pregnancy. Counseling should also include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see the Perinatal Guidelines).

Antiretroviral Regimen Considerations for Individuals Who Are Trying to Conceive or Who Cannot Use Effective Contraception

Efavirenz (EFV) is teratogenic in nonhuman primates. However, a meta-analysis that included data from 23 studies found no evidence for an increased risk of birth defects in infants born to women who received EFV during the first trimester compared with infants born to women who received other ARV drugs during the first trimester.[22] EFV can be used in individuals of childbearing potential who are not using effective contraception or who are contemplating pregnancy. Individuals who become pregnant on EFV-containing regimens should continue their current regimens.

Preliminary data from a study in Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving dolutegravir (DTG) at the time of conception.[23,24] Updated results have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower (0.3%) than reported in the preliminary data, but still higher than in infants who were exposed to ART that did not contain DTG (0.1%).[25,26] Providers should discuss with individuals of childbearing potential the potential risks and benefits of taking DTG and provide appropriate counseling so that individuals can make informed decisions.

Before initiating an integrase strand transfer inhibitor (INSTI)-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen. The key recommendations are listed below:

- **For individuals who are trying to conceive**, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating one of the following regimens, which are designated as *Preferred*

regimens during pregnancy in the Perinatal Guidelines: RAL, atazanavir/ritonavir, or darunavir/ritonavir plus TDF/emtricitabine, TDF/lamivudine (3TC), or ABC/3TC. DTG would be an *Alternative*, rather than a *Preferred*, option **(BII)**.

- **For individuals who are not planning to conceive but who are sexually active and not using contraception**, consider a regimen's effectiveness and tolerability, the available data on potential teratogenicity, and the person's preferences (e.g., pill burden) when choosing between regimens that are recommended for initial therapy (see Table 6a). In this situation, DTG would be an *Alternative*, rather than *Preferred*, option **(BII)**. If the person becomes pregnant, changes to the ARV regimen may be warranted. Clinicians should refer to the Perinatal Guidelines for recommendations.
- **For individuals who are using effective contraception**, a DTG-based regimen is one of the recommended options; however, clinicians should discuss the risks and benefits of using DTG with patients to allow them to make informed decisions **(AIII)**.
- An approach similar to that outlined for DTG should be considered for bictegravir-containing ART **(AIII)**.

In a person with multidrug-resistant HIV who has no alternatives to DTG, the decision of whether to initiate or continue DTG should be made after carefully considering the risk of NTDs in the infant if pregnancy occurs while a patient is taking DTG, the risks of persistent viremia in the patient, and potential HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.

Reproductive Options for Serodiscordant Couples

An individual who wishes to conceive with a serodiscordant partner should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include screening and treating both partners for sexually transmitted infections (STIs), the use of ART to maximally suppress and maintain the viral load of the partner with HIV, the use of pre-exposure prophylaxis by the partner without HIV,[27-29] male circumcision, and/or self-insemination with the sperm of the partner without HIV during the periovulatory period of the individual with HIV.[30]

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unplanned pregnancies and perinatal transmission of HIV are an essential component of care for individuals with HIV of childbearing age. These individuals should receive ongoing counseling on reproductive issues. Regardless of hormonal contraceptive use, individuals with HIV should be advised to consistently use condoms (male or female) during sex and to adhere to an HIV regimen that effectively maintains viral suppression. Both strategies are crucial to prevent transmission of HIV to partners without HIV and to protect against infection with other STIs. The following sections describe some factors to consider when hormonal contraceptives are used.

Drug-Drug Interactions

PK interactions between ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, there are limited clinical data regarding interactions between ARV drugs and hormonal contraceptives, and the clinical implications of these interactions are unclear. The magnitudes of changes in drug concentrations that may reduce contraceptive efficacy or increase the risk of adverse effects are not known for all forms of contraceptives.

- **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 21a, 21b, and 21d), which potentially decreases contraceptive efficacy or increases the risk of estrogen- or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCs that contain ethinyl estradiol and norgestimate.[31] Several regimens that include

a cobicistat-boosted PI, PI/r, or EVG/c decrease oral contraceptive estradiol levels.[32-35] One PK study showed that DTG did not affect ethinyl estradiol or norgestimate levels.[36] Several studies have shown that the use of etravirine, rilpivirine, and NVP did not significantly affect estradiol or progestin levels in individuals with HIV who were using COCs.[37-39]

- **Injectable Contraceptives:** Small studies of women with HIV who were receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, lopinavir/ritonavir (LPV/r), NVP, nelfinavir, or NRTI drugs.[40-43]
- **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.[44,45] Studies of women with levonorgestrel- and etonogestrel-releasing implants reported that participants who received EFV-based ART had decreased bioavailability of levonorgestrel and etonogestrel.[46-48] These studies did not identify any change in hormone concentrations when the implants were used in those taking NVP[46,48] or LPV/r.[47] Similarly, two retrospective cohort evaluations that were conducted in Swaziland and Kenya showed an increased risk of contraceptive failure in women using contraceptive implants and receiving EFV.[49,50]

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARV drugs should not prevent clinicians from prescribing hormonal contraceptives for individuals on ART who prefer this contraceptive method. However, an alternative or additional effective contraceptive method is recommended when there are significant drug interactions between hormonal contraceptives and ARV drugs (see Tables 21a, 21b, and 21d and the Perinatal Guidelines).

Risk of HIV Acquisition and Transmission

Studies have produced conflicting data on the association between hormonal contraception and the risk of acquisition of HIV.[51] Most of the retrospective studies involved couples in which the partners with HIV were not taking ART. A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the partner with HIV was not receiving ART found that, compared to women who did not use hormonal contraception, those using hormonal contraception (the majority of study participants were using injectable DMPA) had a two-fold increased risk of acquiring or transmitting HIV. Higher genital HIV RNA concentrations have been found in women with HIV who were using hormonal contraception than in those who were not using hormonal contraceptives.[52] Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women who were using oral contraceptives in this study was insufficient to adequately assess risk.

A World Health Organization expert group reviewed all available evidence regarding hormonal contraception use and HIV transmission to a partner without HIV and recommended that individuals with HIV can continue to use all existing hormonal contraceptive methods without restriction.[53] Further research is needed to definitively determine whether hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV, particularly in the setting of ART. Regardless, the potential association between hormonal contraception use and HIV transmission in the absence of ART underscores the importance of ART-induced viral suppression to reduce transmission risk.

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for individuals with HIV.[54-56] Although studies have focused primarily on IUDs that do not contain hormones (e.g., copper IUDs), several small studies have found that levonorgestrel-releasing IUDs are also safe and are not associated with increased genital tract shedding of HIV.[57-59]

Pregnancy

Clinicians who are caring for pregnant adults and adolescents with HIV should review the Perinatal Guidelines. The use of combination ARV regimens is recommended for all pregnant persons with HIV,

regardless of virologic, immunologic, or clinical parameters, for their own health and to prevent HIV transmission to the fetus **(AI)**. Pregnant individuals with HIV should be counseled regarding the known benefits and risks of using ARV drugs during pregnancy to the woman, fetus, and newborn. They should be strongly encouraged to receive ART for their own health and their infants' health. Open, nonjudgmental, and supportive discussion should be used to encourage them to adhere to care.

Prevention of Perinatal HIV Transmission

The use of ART and the resultant reduction of HIV RNA levels decrease the risk of perinatal HIV transmission.[60-62] The goal of ART is to achieve maximal and sustained viral suppression throughout pregnancy. Long-term follow-up is recommended for all infants who were exposed to ART *in utero*, regardless of the infant's HIV status (see the Perinatal Guidelines).

Antiretroviral Regimen Considerations

Pregnancy should not preclude the use of optimal ARV regimens. As in nonpregnant individuals, genotypic resistance testing is recommended for all pregnant persons before initiating ARV drugs **(AIII)** and for those with detectable HIV RNA while on ART **(AI)**. However, ART initiation should not be delayed pending genotypic resistance test results. The ARV regimen can be modified, if necessary, once the resistance test results are available **(BIII)**. Unique considerations that influence recommendations on the ARV drugs to use during pregnancy include the following:

- Physiologic changes that are associated with pregnancy and that potentially change the PKs of ARV drugs, which may affect ARV dosing at different stages of pregnancy;
- Potential ARV-associated adverse effects in pregnancy;
- Potential for nonadherence to a particular regimen during pregnancy; *and*
- Potential short-term and long-term effects of an ARV drug on the fetus and newborn, which are unknown for many drugs.

ART is considered the standard of care for pregnant individuals with HIV, both to treat HIV infection and prevent perinatal transmission of HIV. Clinicians should review the Perinatal Guidelines for ARV drug recommendations, including recommendations on the use of DTG and other INSTIs, for individuals who have recently received an HIV diagnosis or those who become pregnant while on ART.

If maternal HIV RNA is ≥1,000 copies/mL (or unknown) near delivery, IV infusion of ZDV during labor is recommended regardless of the mother's antepartum regimen and resistance profile and the mode of infant delivery **(AI)**. Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be administered with sips of water during this time).

Clinicians who are treating pregnant individuals with HIV are strongly encouraged to report cases of prenatal exposure to ARV drugs (either administered alone or in combination) to the Antiretroviral Pregnancy Registry. The registry collects observational data regarding exposure to Food and Drug Administration-approved ARV drugs during pregnancy to assess potential teratogenicity.

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Individuals with HIV should be counseled to avoid breastfeeding; maternal ART reduces, but does not eliminate, the risk of HIV transmission of HIV in breast milk, and postnatal transmission can occur despite maternal ART.[63] Persons with HIV should not premasticate food and feed it to their infants, because the practice has been associated with transmission of HIV.[64] ART is currently recommended for all individuals with HIV **(AI)**; therefore, maternal ART should be continued after delivery. For more information regarding postpartum management of HIV, refer to the Perinatal Guidelines.

Several studies have demonstrated that adherence to ART may decline during the postpartum period.[65-67] Clinicians should address ART adherence at each postpartum clinic visit, including an evaluation of specific factors that facilitate adherence or that present a barrier to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to the Continuum of Care).

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Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B/HIV Virus Coinfection (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations

- Before initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication **(AIII)**.
- Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an ART regimen for patients with both HIV and HBV should be include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**.
- If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen **(BI)**. Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to patients with HBV/HIV-coinfection **(AII)**. Peginterferon alfa monotherapy may also be considered in certain patients **(CII)**.
- Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudine, **are not recommended** for patients with HBV/HIV coinfection **(CII)**.
- Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against stopping these medications and be carefully monitored during interruptions in HBV treatment **(AII)**.
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. Persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Approximately 5% to 10% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection.[1] The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV coinfection than in persons with chronic HBV monoinfection.[2] Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte (CD4) cell responses following initiation of antiretroviral therapy (ART).[3,4] However, antiretroviral (ARV) drug toxicities or several liver-associated complications attributed to flares in HBV activity after initiation or discontinuation of dually active ARV drugs can affect the treatment of HIV in patients with HBV/HIV coinfection.[5-7] These complications include the following:

- Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are ARVs approved to treat HIV that are also active against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV.[8]
- The anti-HBV drug entecavir has activity against HIV. However, when entecavir is used to treat HBV in patients with HBV/HIV coinfection who are not on ART, the drug may select for the M184V

mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in patients with HBV/HIV coinfection, entecavir must be used in addition to a fully suppressive ARV regimen **(AII)**.[9]

- When 3TC is the only active drug used to treat chronic HBV in patients with HBV/HIV coinfection, 3TC-resistant HBV emerges in approximately 40% and 90% of patients after 2 and 4 years on 3TC, respectively. Therefore, 3TC or FTC, which is similar to 3TC, should be used in combination with other anti-HBV drugs **(AII)**.[10]
- In patients with HBV/HIV coinfection, immune reconstitution following initiation of treatment for HIV, HBV, or both can be associated with elevated transaminase levels, possibly because HBV-induced liver damage is primarily an immune-mediated disease.[11]
- Some ARV agents can increase transaminase levels. The rate and magnitude of these increases are higher with HBV/HIV coinfection than with HIV monoinfection.[12-14] The etiology and consequences of these changes in liver function tests are unclear because the changes may resolve with continued ART. Nevertheless, some experts suspend the suspected agent(s) when the serum alanine transferase (ALT) level increases to 5 to 10 times the upper limit of normal or at a lower threshold if the patient has symptoms of hepatitis. However, increased transaminase levels in persons with HBV/HIV coinfection may indicate hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution; thus, the cause of the elevations should be investigated before discontinuing medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe, as well as HBV DNA levels.

Recommendations for Patients with HBV/HIV Coinfection

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see Hepatitis B Virus Infection in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents). Patients with chronic HBV should also be tested for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and, if nonimmune, receive the HAV vaccination. In addition, patients with chronic HBV should be advised to abstain from alcohol and counseled on prevention methods that protect against both HBV and HIV transmission.[15]
- Before ART is initiated, all persons who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication **(AIII)**, and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) is to prevent liver disease complications by sustained suppression of HBV replication.
- Since HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment,[16,17] persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes agents with anti-HBV activity (such as [TDF or TAF] plus [FTC or 3TC]) prior to initiating HCV therapy **(AIII)**. The diagnosis of HBV reactivation should be considered in persons with current HBV infection who experience elevated liver enzymes during or immediately after HCV therapy.

Antiretroviral Drugs with Dual Activities against HBV and HIV

Among the ARV drugs, 3TC, FTC, TAF, and TDF all have activity against HBV. Entecavir is an HBV nucleoside analog which also has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF.

The efficacy of TDF versus TAF in patients with HBV monoinfection was evaluated in a randomized controlled trial of HBV treatment-naive and treatment-experienced HBeAg-negative patients. In this study,

TAF was noninferior to TDF based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = .47$).[18] TAF was also noninferior to TDF in HBeAg-positive patients with chronic HBV monoinfection with a similar percentage of patients achieving HBV DNA levels <29 IU/mL at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = .25$).[19] In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to 48 weeks also favored TAF.[18,19]

In patients with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy

The combination of (TAF or TDF) plus (3TC or FTC) should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection **(AII)**.[20-22] The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and for acceleration of bone loss. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ART regimen to the fixed-dose combination elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/c/TAF/FTC) maintained or achieved HBV suppression, with improved eGFR and bone turnover markers.[23] TAF/FTC-containing regimens currently approved for the treatment of HIV infection are not recommended for use in patients with creatinine clearance (CrCl) <30 mL/min. While data on switching from a TDF-based to a TAF-based ART regimen are limited, the data from the EVG/c/TAF/FTC switch study suggest that patients with HBV/HIV coinfection can switch to TAF/FTC-containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy

If TDF or TAF cannot safely be used, entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; however, entecavir should not be considered as part of the ARV regimen (BII).[24] Because entecavir and 3TC share a partially overlapping pathway to HBV resistance, it is unknown whether the combination of entecavir plus 3TC or FTC will provide greater virologic or clinical benefit than entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (approximately every 3 months) of the HBV DNA level to detect viral breakthrough.

Peginterferon alfa monotherapy for up to 48 weeks may also be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in persons with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in persons with HBV/HIV coinfection who have decompensated cirrhosis.

HBV Drugs Not Recommended

Other HBV treatment regimens include telbivudine used in addition to a fully suppressive ARV regimen, or adefovir used in combination with 3TC or FTC and a fully suppressive ARV regimen.[20,25,26] However, data on these regimens in persons with HBV/HIV coinfection are limited. In addition, these regimens are associated with higher rates of HBV treatment failure and a higher incidence of toxicity when compared to regimens containing TDF, TAF, or entecavir. These toxicities include increased risk of renal disease with adefovir-containing regimens and increased risk of myopathy and neuropathy with telbivudine-containing regimens. Therefore, the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents **does not currently recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

Changing Antiretroviral Therapy

- **Need to discontinue ARV medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve such as those with compensated or decompensated cirrhosis.[8] These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.
- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other ARV agents that effectively suppress HIV **(AIII)**.

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Hepatitis C Virus/HIV Coinfection (Last updated December 18, 2019; last reviewed December 18, 2019)

Panel's Recommendations
• All people with HIV should be screened for hepatitis C virus (HCV) infection **(AIII)**. Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII)**.
• Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most persons with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count **(AI)**.
• Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug-drug interactions and overlapping toxicities **(AIII)** (see discussion in the text below and in Table 15).
• All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes assessing their liver fibrosis stage to guide the duration of therapy and predict subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII)**.
• Persons with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or Immunoglobulin G). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination **(AIII)**.
• HBV reactivation has been observed in persons with HBV infection during HCV treatment with direct-acting antivirals (DAAs). Accordingly, before initiating HCV therapy, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV activity **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. Patients with HCV/HIV coinfection treated with all-oral, direct-acting antiviral (DAA) HCV regimens can achieve sustained virologic response (HCV cure) at rates comparable to those in patients with HCV mono-infection.[1-3] This section of the guidelines focuses on hepatic safety and drug-drug interaction issues related to HCV/HIV coinfection and the concomitant use of antiretroviral (ARV) agents and HCV drugs. For specific guidance on HCV treatment, clinicians should refer to the HCV Guidance from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

Approximately one-third of patients with chronic HCV infection progress to cirrhosis, at a median time of <20 years.[4,5] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[6-9] A meta-analysis found that patients with HCV/HIV coinfection had a three-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV mono-infection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV coinfection, several studies have demonstrated that the rate of disease progression continues to exceed that observed in patients without HIV infection.[10,11] Whether HCV infection accelerates HIV progression, as measured by the occurrence of AIDS-related opportunistic infections (OIs) or death,[12] is unclear. With older ARV drugs, persons with HIV and HCV coinfection experienced higher rates of hepatotoxicity than those seen in persons with HIV but not HCV.[13,14] These higher rates have not been observed with the newer ARV agents that are currently in use.

Assessment of HCV/HIV Coinfection

- All patients with HIV should be screened for HCV infection using sensitive immunoassays licensed for the detection of antibodies to HCV in blood.[15] At-risk HCV-seronegative patients should undergo repeat testing annually or as clinically indicated. HCV-seropositive patients should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection. Patients who test HCV RNA positive should undergo HCV genotyping and liver disease staging as recommended by the HCV Guidance.
- Persons with HCV/HIV coinfection should be counseled to avoid consuming alcohol.
- Persons with HCV/HIV coinfection should be also be counseled about appropriate precautions to prevent transmission of HIV and/or HCV to others.
- People with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or Immunoglobulin G).
  - Persons with evidence of active HBV infection (HBsAg positive) should be further evaluated and treated with ART that includes agents with anti-HIV and anti-HBV activities **(AIII)**.
  - Those who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination.
- Patients with HCV/HIV coinfection who are susceptible to hepatitis A virus (HAV) should be vaccinated against HAV.
- All patients with HCV/HIV coinfection are candidates for curative HCV treatment.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for persons with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, considering the need for concurrent HCV treatment with oral DAA regimens, the potential for drug-drug interactions, and the individual's HBV status.

Considerations When Starting Antiretroviral Therapy

The same regimens that are recommended for initial treatment of HIV in most ART-naive persons are also recommended for persons with HCV/HIV coinfection. Special considerations for ARV selection in persons with HCV/HIV coinfection include the following:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions with the HCV treatment regimen (see Table 15).
- In persons with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, before initiating HCV therapy, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) **(AIII)**.
- Patients with cirrhosis should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 10).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in patients with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV coinfection who have advanced liver disease (e.g., cirrhosis, end-stage liver disease) are at greatest risk for DILI.[18] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[19] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and more often if clinically indicated. Mild to moderate fluctuations in ALT and/or AST levels (<5 times upper limit of normal [ULN]) are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART, but do warrant monitoring to ensure a return to baseline. Patients with significant elevations in ALT and/or AST levels (>5 times ULN), concomitant increase in total bilirubin, and/or concomitant symptoms (weakness, nausea, vomiting) should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis). If these signs and symptoms do not resolve, ART should be discontinued.

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug-drug interactions when used in combination. Before starting HCV therapy, the ART regimen may need to be modified to reduce the drug-drug interaction potential. Table 15 below provides recommendations on the concomitant use of selected drugs for the treatment of HCV and HIV infection. In patients receiving ART that has been modified to accommodate HCV treatment, HIV RNA should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After ART modification, initiation of an HCV DAA regimen should be delayed for ≥2 weeks. Resumption of the original ART regimen should also be delayed until ≥2 weeks after the HCV DAA regimen is completed. The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug-drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV (page 1 of 4)

The recommendations in this table for concomitant use of select HIV drugs with FDA-approved HCV DAA drugs are based on available PK interaction data or are predictions based on the known metabolic pathways of the agents. (Instances where PK interaction data are limited or not available are indicated in the table.) Whenever HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and the HCV Guidance for updated information.

Note: Interactions with FPV, IDV, NFV, and SQV are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV PIs.

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	NS5A Inhibitor	NS5B Inhibitor	Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
			NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/NS3/4A PI	NS5A Inhibitor/ NS3/4A PI	NS5A Inhibitor/ NS3A/4A PI	NS5A Inhibitor/NS3A/4A PI plus NS5B Inhibitor
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/RTV plus Dasabuvir[a]
NRTIs								
3TC	✓	✓	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF-associated adverse events.	✓ Monitor for TDF-associated adverse events.	✓ Monitor for TDF-associated adverse events.	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓	✓	✓
PIs								
Unboosted ATV	✓	✓	✓	✓	×	×	×	✓[b]

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV (page 2 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	NS5A Inhibitor	NS5B Inhibitor	Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
			NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/NS3/4A PI	NS5A Inhibitor/ NS3/4A PI	NS5A Inhibitor/ NS3A/4A PI	NS5A Inhibitor/NS3A/4A PI plus NS5B Inhibitor
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/RTV plus Dasabuvir[a]
PIs, continued								
ATV/r or ATV/c	✓ ↓ daclatasvir dose to 30 mg/day	✓	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated adverse events.[d]	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated adverse events.[d]	×	×	×	✓[c]
DRV/r or DRV/c	✓	✓			✓ If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor for TDF-associated adverse events.[d] Consider monitoring for hepatotoxicity.[e]	×	×	×
LPV/r	✓	✓			×	×	×	×
TPV/r	?	×	×	×	×	×	×	×
NNRTIs								
DOR	✓	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓	✓
EFV	✓ ↑ daclatasvir dose to 90 mg/day	✓		×	×	×	×	×
ETR	✓ ↑ daclatasvir dose to 90 mg/day	✓		×	×	×	×	×
NVP	✓ ↑ daclatasvir dose to 90 mg/day	✓		×	×	✓[f]	×	×

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV (page 3 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents							
	NS5A Inhibitor	NS5B Inhibitor	Coformulated					
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)			
			NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/NS3/4A PI	NS5A Inhibitor/ NS3/4A PI	NS5A Inhibitor/ NS3A/4A PI	NS5A Inhibitor/NS3/4A PI plus NS5B Inhibitor
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/Paritaprevir/RTV plus Dasabuvir[a]
NNRTIs, continued								
RPV	✓	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓	×
INSTIs								
BIC/TAF/FTC	✓	✓	✓	✓	✓	✓	✓	✓
DTG	✓	✓	✓ If used with TDF, monitor for TDF-associated adverse events.	✓	✓	✓	✓	✓
EVG/c/TDF/ FTC	✓ ↓ daclatasvir dose to 30 mg/day	✓	×	✓ If used with TDF, monitor for TDF-associated adverse events.	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[e]	✓ If used with TDF, monitor for TDF-associated adverse events. Consider monitoring for hepatotoxicity.[g]	×	×
EVG/c/TAF/ FTC	✓ ↓ daclatasvir dose to 30 mg/day	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[e]	✓ Consider monitoring for hepatotoxicity.[g]	×	×
RAL	✓	✓	✓	✓	✓	✓	✓	✓
CCR5 Antagonist								
MVC	✓	✓	✓	✓	✓	✓	✓	×

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C Virus in Adults with HIV (page 4 of 4)

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/RTV.

[b] Reduce ATV dose to 300 mg and instruct the patient to take it in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.

[c] This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg without COBI or RTV. The modified ARV regimen should be taken in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.

[d] Consider using an alternative HCV treatment or ARV regimen to avoid increases in TDF exposure. If coadministration is necessary, monitor patient for TDF-associated adverse events.

[e] Voxilaprevir exposures can increase when it is coadministered with pharmacologically boosted DRV or EVG. Until more safety data in clinical settings becomes available, patients who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

[f] Consider alternative ARV or HCV regimen. If used together, monitor for HCV efficacy.

[g] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings becomes available, patients who are receiving glecaprevir and EVG/c should be monitored for hepatotoxicity.

Key to Symbols:

✓ = ARV agents that can be used concomitantly

× = ARV agents not recommended

? = Data on PK interactions with ARV drug are limited or not available

↑ = Increase

↓ = Decrease

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; COBI = cobicistat; DAA = direct-acting antiviral agents; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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Tuberculosis/HIV Coinfection (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- Selection of tuberculosis (TB)-preventive treatment for individuals with HIV and latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:
  - Any ART regimen can be used when isoniazid alone is used for LTBI treatment **(AIII)**.
  - Efavirenz 600 mg once daily- or raltegravir 400 mg twice daily-based regimens (in combination with either abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) can be used without dose adjustment with once-weekly isoniazid plus rifapentine **(AII)**.
  - If rifampin or rifapentine is used to treat LTBI, clinicians should review Tables 21a through 21e to assess the potential for drug-drug interactions among different antiretroviral (ARV) drugs and the rifamycins **(AIII)**.
- All patients with HIV and active TB who are not on ART should be started on ART as described below:
  - **CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.
  - **CD4 counts ≥50 cells/mm^3:** Initiate ART within 8 weeks of starting TB treatment **(AI)**.
  - **During pregnancy, regardless of CD4 count:** Initiate ART as early as feasible, for treatment of the person with HIV and to prevent HIV transmission to the infant **(AIII)**.
  - **With tuberculous meningitis:** When initiating ART early, patients should be closely monitored as high rates of adverse events and deaths have been reported in a randomized trial **(AI)**.
- For patients with active TB who are receiving ART, the ARV regimen should be assessed with particular attention to potential drug-drug interactions between ARVs and TB drugs. The ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 21a through 21e for dosing recommendations).
- Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), are critical components of TB treatment regimens and should be included in regimens for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycin antibiotics have a considerable potential for drug-drug interactions. Clinicians should review Tables 21a through 21e to assess the potential for interactions among different ARV drugs and the rifamycins **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Managing Latent Tuberculosis Infection in Persons with HIV

Approximately 23% of the world's population has tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.[1] Among individuals with TB infection, the risk of developing active TB is much higher among those who also have HIV, and this risk increases as immune deficiency worsens.[2]

Tuberculosis Preventive Treatment

Randomized controlled clinical trials have demonstrated that treatment for latent tuberculosis infection (LTBI) in people with HIV reduces risk of active TB, especially in those with a positive tuberculin skin test.[3] After active TB disease has been excluded, the Centers for Disease Control and Prevention (CDC) recommends one of the following regimens for LTBI treatment (see Treatment Regimens for Latent TB Infection (LTBI), Adult and Adolescent Opportunistic Infection Guidelines):

- Isoniazid daily or twice weekly for 6 or 9 months
- Isoniazid plus rifapentine once weekly for 12 weeks
- Rifampin daily for 4 months.

For more than 30 years, isoniazid has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadminstered with any antiretroviral (ARV) regimen. The combination of isoniazid and rifapentine administered once a week for 12 weeks as directly observed therapy (DOT) was as safe and effective as 9 months of isoniazid alone in preventing TB in patients with HIV who were not on ART in the PREVENT

TB study.[4] Another study randomized 1,148 South African adults with HIV to one of four treatment groups: rifapentine plus isoniazid weekly for 12 weeks, rifampin plus isoniazid twice weekly for 12 weeks, isoniazid daily for 6 months, or continuous isoniazid therapy. TB incidence did not differ among the groups.[5] Similarly, in 3,000 people with HIV infection in the BRIEF TB study, there was no difference in TB incidence between those who received rifapentine plus isoniazid daily for 1 month and those who received 9 months of daily isoniazid.[6] There were fewer adverse events and a higher treatment completion rate with the 1-month regimen than with 9 months of isoniazid alone. However, this short-course regimen has not yet been endorsed by the World Health Organization or CDC.

Although rifapentine induces cytochrome P (CYP) 450 isoenzymes and can potentially cause significant drug-drug interactions, there are pharmacokinetic (PK) data supporting its use, daily or once weekly with efavirenz (EFV) 600 mg daily,[7,8] and once weekly with raltegravir (RAL) 400 mg twice daily **(AII)**.[9] A healthy volunteer study of dolutegravir (DTG) and weekly rifapentine with isoniazid was stopped early following the development of an influenza-like syndrome and elevated aminotransferase levels in two of the first four participants after the third rifapentine-isoniazid dose.[10] However, in a Phase 1/2 study of 60 adults with HIV on DTG-based ART and weekly rifapentine with isoniazid, coadministration of the regimens was well tolerated.[11] Although the rifapentine-isoniazid regimen decreased DTG trough concentrations by 50% to 60%, all but one remained above the DTG IC_{90} and all HIV viral loads remained suppressed. Until more clinical data are available on the safety and efficacy of DTG use with rifapentine, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) does not recommend DTG use with once weekly rifapentine-isoniazid **(AIII)**. Rifampin for 4 months may also be considered for TB preventive treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 21a through 21e).

A randomized trial of isoniazid preventive therapy (IPT) that compared isoniazid initiated during pregnancy (immediate IPT) to delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART. This study demonstrated a greater number of adverse pregnancy outcomes in women on immediate IPT. Treatment-related maternal adverse events were higher than expected in both arms, suggesting that IPT should be delayed until after delivery.[12] IPT is still recommended, however, for pregnant women with HIV whose close household contacts include a person with TB disease (Adult and Adolescent Opportunistic Infection Guidelines).

If a patient with HIV is a contact of an individual with drug-resistant TB, the options for LTBI treatment should be modified. In this setting, consultation with a TB expert is advised.

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Accumulating evidence suggests that ART can prevent active TB. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV to one of four study arms: deferred ART, deferred ART plus IPT, early ART, or early ART plus IPT. The initial results demonstrated that IPT and early ART each independently reduced the risk of a serious HIV-related event, many of which were tuberculosis, and that IPT with early ART provided the best protection from disease.[13] Data from longer follow-up (median 4.9 years) showed that 6 months of IPT given early in the course of HIV infection provided a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART.[14] In the START study, 4,685 participants with CD4 T lymphocyte (CD4) cell counts >500 cells/mm^3 were randomized to receive immediate ART or ART deferred until their CD4 count dropped to 350 cells/mm^3 or until they developed a clinical condition that required ART. TB was one of the three most common clinical events, occurring in 14% of participants in the immediate ART group and 20% of participants in the deferred ART group.[15] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with high prevalence of TB/ HIV coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in patients with HIV should follow the general principles guiding treatment for patients without HIV. The Adult and Adolescent Opportunistic Infection Guidelines include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV.

All patients with HIV/TB disease should be treated with ART **(AI)** though the timing of initiation of ART may vary as discussed below. Important considerations related to the use of ART in patients with active TB disease include:

- When to start ART;
- Significant PK drug-drug interactions between anti-TB and ARV agents;
- The additive toxicities associated with concomitant ARV and anti-TB drug use; *and*
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Tuberculosis Diagnosed While a Patient is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a patient receiving ART, but the ARV regimen should be assessed with particular attention to potential drug interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 18a through 18e for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality rates in the SAPiT-1 study.[16] The timing of ART in specific patient populations is discussed below.

Patients with CD4 Counts <50 cells/mm^3: Three large randomized clinical trials in patients with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm^3 significantly reduced AIDS events or deaths.[17-19] In these studies, early ART was defined as starting ART within 2 weeks of and no later than 4 weeks after initiation of TB therapy. In all three studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 counts <50 cells/mm^3 **(AI)**.

Patients with CD4 Counts ≥50 cells/mm^3: In the three studies mentioned above,[17-19] there was no survival benefit for patients with CD4 counts ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in patients with TB and CD4 counts >50 cells/mm^3. However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the Panel recommends ART initiation within 8 weeks of starting TB treatment for patients with CD4 counts ≥50 cells/mm^3 **(AI)**.

Patients with Drug-Resistant TB: Mortality rates in patients with multidrug-resistant or extensively drug-resistant TB and HIV are very high.[20] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients,[21,22] but the optimal timing for initiation of ART is unknown. Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(BIII)**.

Patients with TB Meningitis: TB meningitis is often associated with severe complications and a high

mortality rate. In a study conducted in Vietnam, patients with HIV-associated TB meningitis were randomized to immediate ART or to ART deferred until 2 months after initiation of TB treatment. A significantly higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).[23] Despite these study results, many experts would recommend initiating ART within 2 to 8 weeks of starting anti-TB treatment, opting for 2 weeks in individuals with CD4 counts <50 cells/mm^3 in settings in which close monitoring of drug-related toxicities and central nervous system adverse events is feasible (see Adult and Adolescent Opportunistic Infection Guidelines) **(BIII)**. Managing patients with HIV and TB meningitis is complex, and expert consultation is encouraged **(BIII)**.

Pregnant Patients: All pregnant individuals with HIV and active TB should be started on ART as early as feasible, both for treatment of the person with HIV and to prevent HIV transmission to the infant **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and should take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).

Drug Interaction Considerations

Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), are a crucial component of TB treatment regimens. However, they are associated with a considerable potential for drug interactions. Rifampin is a potent inducer of the hepatic CYP450 (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 enzymes. Rifabutin and rifapentine are CYP3A4 substrates and inducers. As potent enzyme inducers, the rifamycin antibiotics can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs), and the CCR5 antagonist maraviroc (MVC). Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs), the fusion inhibitor enfuvirtide, and the CD4 post attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. Tables 21a through 21e outline the magnitude of these interactions and provide dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because tenofovir alafenamide (TAF) is a P-gp substrate, its plasma concentrations may be reduced by rifamycin antibiotics. Current labeling does not recommend concomitant administration of TAF and any rifamycin antibiotic.[24] However, in a healthy volunteer study, following administration of TAF/emtricitabine with rifampin, intracellular tenofovir-DP concentrations were still 4.2-fold higher than those achieved by tenofovir disoproxil fumarate.[25] A clinical trial in persons with HIV and TB with concomitant use of TAF and rifampin is ongoing.

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to Tables 21a through 21e before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. The Phase 3 REFLATE TB2 trial compared ARV regimens including standard dose RAL 400 mg twice daily or EFV 600 mg once daily for the treatment of HIV/TB coinfection. At week 48, the standard dose RAL 400 mg twice daily regimen did not demonstrate noninferiority to EFV 600 mg once daily.[26] In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.[27,28] Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in patients weighing >50 kg,[29] this dosage increase is generally not necessary. A reduced dose of EFV 400 mg once daily is now approved for HIV treatment. Coadministration of EFV 400 mg with rifampin and isoniazid led to only limited changes in EFV AUC (<25%) in a study with 26 participants with HIV infection, and plasma concentrations were considered adequate to maintain virologic suppression.[30] Until more clinical trial data are available regarding the safety and efficacy of EFV 400 mg, the Panel continues to recommend EFV 600 mg for individuals receiving

rifampin therapy.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 21a through 21e for dosing recommendations).

Rifapentine is a long-acting rifamycin which, when given daily, is a more potent inducer than rifampin.[31] Once-daily rifapentine did not affect the oral clearance of EFV in individuals with HIV in the BRIEF TB study,[32] and once weekly rifapentine has minimal impact on EFV exposure.[7] Once-weekly rifapentine led to an increase rather than a decrease in RAL drug exposure in healthy volunteers.[9] Once-weekly isoniazid plus rifapentine for LTBI treatment should only be given to patients receiving either an EFV 600 mg-, or RAL-based regimen **(AII)**.

After selecting the ARV drugs and rifamycin to use, clinicians should determine the appropriate dose of each, and should closely monitor the patients to assure good control of both TB (when treating active TB) and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, adequacy of drug exposure, or presence of acquired HIV or TB drug resistance.

Tuberculosis-Associated IRIS

IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). TB-associated IRIS (TB-IRIS) has been reported in 8% to >40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[33,34] Predictors of IRIS include a baseline CD4 count <50 cells/mm^3; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and <30-day interval between initiation of TB and HIV treatments.[35] Most IRIS in HIV/TB disease occurs ≤3 months of the start of ART.

Manifestations of unmasking TB-IRIS are characterized by their marked inflammatory nature, such as high fever, respiratory distress, lymphadenitis, abscesses, and sepsis syndrome. Manifestations of paradoxical TB-IRIS include fevers, new or worsening lymphadenopathy, new or worsening pulmonary infiltrates, enlarging pleural effusions, and new or enlarging tuberculomas.

In general, the Panel recommends continuing ART without interruption during IRIS **(AIII)**.

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Limitations to Treatment Safety and Efficacy

Adherence to the Continuum of Care (Last reviewed October 17, 2017)

Key Summary of Adherence to the Continuum of Care

- Linkage-to-care and adherence to both antiretroviral therapy (ART) and clinic appointments should be regularly assessed.
- An individual's barriers to adherence to ART and appointments should be assessed before initiation of ART and regularly thereafter.
- Patients with ART adherence problems should be placed on regimens with high genetic barriers to resistance, such as dolutegravir (DTG) or boosted darunavir (DRV). Side effects, out-of-pocket costs, convenience, and patient preferences also need to be considered.
- Patients having difficulties with adherence to appointments or ART should be approached in a constructive, collaborative, nonjudgmental, and problem-solving manner.
- The approach to improved adherence should be tailored to each person's needs (or barriers to care). Approaches could include, but are not limited to:
  - Changing ART to simplify dosing or reduce side effects
  - Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
  - Allowing flexible appointment scheduling
  - Assisting with transportation, or
  - Linking patients to counseling to overcome stigma, substance use, or depression.
- Multidisciplinary approaches to find solutions to ART and appointment adherence problems are often necessary, including collaboration with social work and case management (to the extent available). The clinician's role is to help the patient understand the importance of adherence to the continuum of care and reveal barriers to adherence, and link the patient to resources to overcome those barriers.
- A summary of best practice interventions to improve linkage, retention, and adherence can be found at a Centers for Disease Control and Prevention compendium (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

Introduction

Treatment adherence includes initiating care with an HIV provider (linkage to care), regularly attending appointments (retention in care), and adherence to antiretroviral therapy (ART). The concept of a "continuum of care" has been used to describe the process of HIV testing, linkage to HIV care, initiation of ART, adherence to treatment, retention in care, and virologic suppression.[1-3] The U.S. Centers for Disease Control and Prevention (CDC) estimates that HIV has not yet been diagnosed in about 13% of the people living with HIV in the United States. After receiving an HIV diagnosis, about 75% of individuals are linked to care within 30 days. However, only 57% of persons who receive an HIV diagnosis are retained in HIV care. It is estimated that only approximately 55% of persons with diagnosed HIV are virally suppressed because of poor linkage to care and retention in care.[4] The data for adolescents and young adults are even more sobering: only 51% of youth living with HIV receive a diagnosis, 68% are linked to care within 1 month, and 55% are retained in care. As a result, adolescents and young adults had the lowest rate of viral suppression among all age groups, at only 44%.[5] Outcomes along the continuum also vary by geographic region and other population characteristics, such as sex, race/ethnicity, and HIV risk factors.[4] To achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, adherence to each step in the continuum of care is critical.[6] It is also important to realize that retention and adherence are not static states. Life events, changes in insurance status, comorbid conditions and health system changes can cause people to shift back and forth on the continuum. Knowledgeable providers and high-quality system processes are vital in promoting rapid linkage and sustained retention in care and adherence to ART.

This section provides guidance on linking patients to care, assessing and improving retention in care, and assessing and improving adherence to ART. The CDC maintains a compendium of evidence-based

and evidence-informed interventions to improve linkage, retention, and adherence (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html). In addition, a number of other groups and organizations have provided guidance for improving adherence to the steps in the care continuum.[6,7]

Linkage to Care

Receiving a diagnosis of HIV infection can be traumatic and linkage to care efforts must be delivered with sensitivity and persistence. The time from diagnosis to linkage to care can be affected by many factors, including insufficient socioeconomic resources, active substance use, mental health problems, stigma, and disease severity (symptomatic HIV is associated with more successful linkage).[8-12] In the United States, youth, people who use injection drugs, and black/African American persons have lower rates of linkage to care.[4] Some health system-associated factors have also been associated with linkage success or failure. Co-location of testing and treatment services[11] and active linkage services (e.g., assisting the patient in setting up appointments, maintaining an active relationship with the patient until linkage is completed, and providing linkage case management services)[13-15] bolster linkage to care. Conversely, passive linkage (e.g., only providing names and contact information for treatment centers) is associated with lower linkage to care.

Monitoring Linkage to Care

Linking to HIV care after a new diagnosis of HIV infection is defined as completing an outpatient appointment with a clinical provider who has the skills and ability to treat HIV infection, including prescribing ART. Patients should be linked to care as soon as possible after diagnosis with HIV, preferably within 30 days. Monitoring linkage is a critical responsibility so that interventions can effectively reach persons who are not linked to care. If the facilities that diagnose and treat an individual are the same or share the same electronic medical record system, it is relatively straightforward to monitor linkage to care. Monitoring linkage for persons whose HIV is diagnosed outside the treatment provider's healthcare system is difficult and generally is the responsibility of the diagnosing provider/entity and the public health authority. However, once a patient makes contact with the treating clinical system, he or she should be engaged in linkage efforts and monitored for successful linkage to and retention in HIV care.

Improving Linkage to Care

Strategies to improve linkage to care are summarized in Table 16. Linkage efforts should include immediate referral to care at diagnosis, appointment reminders, and outreach efforts if needed.[13] The only intervention shown to increase linkage to care in a randomized trial conducted in the United States is the Anti-Retroviral Treatment and Access to Services (ARTAS) intervention.[14] ARTAS is a strength-based intervention which aims to facilitate linkage to and retention in care for persons with recently diagnosed HIV. The ARTAS intervention was tested in four cities and enrolled a diverse group of persons. The participants in the ARTAS intervention trial were randomized to either an intervention arm or a control arm. Participants randomized to the control arm received information about HIV and care resources and a referral to a local HIV Medical provider. Each participant in the intervention arm worked with an ARTAS interventionist for five sessions, 90 days, or until linkage—whichever came first. The interventionist helped the participant to identify and use his or her strengths, abilities, and skills to link to HIV care, and linked the participant to community resources. Linkage to care, defined as completing at least one visit with an HIV clinician within the first 6 months, was greater among the ARTAS participants than the control participants (78% vs. 60%, adjusted RR = 1.36, $P < 0.001$). Furthermore, a greater percentage of ARTAS participants were retained in care, defined as visiting an HIV clinician at least once in each of the first two 6-month blocks after enrollment (64% vs. 49% for ARTAS and control participants, respectively; adjusted RR = 1.41, $P = 0.006$). ARTAS has been replicated in a community-based study.[15] CDC supports free training in the ARTAS intervention (https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/PublicHealthStrategies/ARTAS.aspx). Other studies support the importance of post-test counseling to educate, motivate, and present positive messages about

living with HIV,[16] peer support,[17] and engaging with the patient at the clinic in advance of the visit with the provider.[18] Financial incentives did not increase linkage to care within 90 days in a large randomized trial.[19]

Retention in Care

Poor retention in HIV care is associated with greater risk of death.[20,21] Poor retention is more common in persons who are substance users, have serious mental health problems, have unmet socioeconomic needs (e.g., housing, food, or transportation), lack financial resources or health insurance, have schedules that complicate adherence, have been recently incarcerated, or face stigma.[22-25] At the provider and health system level, low trust in providers and a poor patient-provider relationship have been associated with lower retention, as has lower satisfaction with the clinic experience.[26-28] Availability of appointments and timeliness of appointments (i.e., long delay from the request for an appointment to the appointment's date) and scheduling convenience are also factors.

Monitoring Retention in Care

Retention in care should be routinely monitored.[6] There are various ways to measure retention, including measures based on attended visits over a defined period of time (constancy measures), and measures based on missed visits.[29] Both approaches are valid and independently predict survival.[30] Missed visits and a prolonged time since last visit are relatively easy to measure and should trigger efforts to retain or re-engage a person in care. Constancy measures (e.g., at least two visits that are at least 90 days apart over 1 year, or at least one visit every 6 months over the last 2 years), can be used as clinic quality assurance measures.

Improving Retention in Care

Strategies to improve retention in care are summarized in Table 16. The Retention through Enhanced Personal Contact (REPC) intervention was tested in a randomized trial in six clinics in the United States. The intervention relied on personal contact by an interventionist with at-risk patients. It included a brief face-to-face meeting upon returning to care and at each clinic visit and three types of phone calls: to check on patients between visits, as appointment reminders just before visits, and to attempt to reschedule missed visits. REPC resulted in small but significant improvements in retention in care, including in racial/ethnic minority populations and persons with detectable plasma HIV RNA.[31] In-clinic opioid replacement therapy helps opioid users remain in care.[32] An intervention using the electronic medical record to alert providers when patients had suboptimal follow-up or high viral loads also improved retention in care.[33] On the other hand, in two randomized trials involving out-of-care, hospitalized patients with HIV, peer counselors and patient navigators did not improve relinkage to care after hospital discharge.[34,35] Data from nonrandomized studies support:

- Clinic-wide marketing (e.g., posters, brochures, and customer service training of patient-facing staff) to promote attending scheduled visits and provide patients a welcoming and courteous experience,[36]
- Stepped case management and social and outreach services,[37] and
- "Data to Care" approaches which use clinic and public health data to reach out-of-care persons and re-engage them into care (see https://effectiveinterventions.cdc.gov/en/highimpactprevention/publichealthstrategies/DatatoCare.aspx).[38-40] However, the effectiveness of "data to care" interventions is variable and privacy concerns must be adequately addressed.

Overall, these data support the concept that all clinic personnel, from the facilities staff to nurses to providers, play important roles in supporting retention in care by providing the optimal patient care experience, constructively affirming attendance rather than criticizing non-attendance, and collaboratively problem solving with patients to overcome barriers to care.[27,31,36] Flexible appointment schedules, expanded clinic hours, and copay and other financial or insurance assistance such as that provided by the Ryan White program will also provide patients with uninterrupted access to clinical care. Guidelines regarding linkage

and retention have been published.[6,7] CDC maintains a compendium of evidence-based and evidence-informed interventions (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

The use of financial incentives or rewards to promote retention in care has been studied. A large study randomized clinic sites to financial incentives or standard-of-care. At baseline, 45% of the patients were retained in care in these clinics. The relative increase in the proportion of participants retained in care was 9% higher in clinics offering incentives than in standard-of-care clinics. Viral suppression also improved 4% at financial incentive clinics, from a baseline of 62%.[19] In another large, randomized study of persons out-of-care and hospitalized, financial incentives plus patient navigation did not lead to sustained improvement in retention or viral load suppression over that achieved with standard care.[34] The use of financial incentives therefore remains experimental and cannot be recommended for routine care at this time.

Adherence to Antiretroviral Therapy

Adherence to ART can be influenced by a number of factors, including the patient's social situation and clinical condition, the prescribed regimen, and the patient-provider relationship.[41] Poor adherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, busy or unstructured daily routines, active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications due to financial and insurance status).[42-44]

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens,[45] including those with low pill burden (even if not one pill once daily), without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[46,47] Single-tablet regimens (STR) that include all antiretrovirals in one pill taken once daily are easier for people to use. However, data to support or refute the superiority of a STR versus a once-daily multi-tablet regimen (MTR), as might be required for the use of some soon-to-be-available generic-based antiretroviral (ARV) regimens, are limited. There are demonstrated beneficial effects on virologic suppression in switch studies, in which persons on MTR are randomized to stay on MTR or switch to STR.[48] Whether an STR is beneficial in treatment-naive patients is not known, with at least one large observational cohort study showing benefit of once-daily STR versus once-daily MTR, but only when switches for simplification of MTR were considered failures.[47,49] Comparisons of these regimens are hampered since not all drugs and classes are available as STR.

Characteristics of the clinical setting can also have important structural influences on the success or failure of medication adherence. Settings that provide comprehensive multidisciplinary care (e.g., by case managers, pharmacists, social workers, and mental health and substance abuse providers) support patients' complex needs, including their medication adherence-related needs. Drug abuse treatment programs are often best suited to address substance use and may offer services that promote adherence, such as directly observed therapy (DOT).

Monitoring Adherence to Antiretroviral Therapy

Adherence to ART should be assessed and addressed in a constructive and nonjudgmental manner at every visit. Given the potency of contemporary ART, a detectable viral load identified during chronic care for a patient with stable access to ART is most likely the result of poor adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool. Carefully assessed patient self-report of high-level adherence to ART has been associated with favorable viral load responses.[50,51] Patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self-report often depends on how the clinician elicits the information. It is most reliable when ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses. To allow patients to disclose lapses in adherence, some experts suggest inquiring about the number of missed doses during a defined time period. For example, for a patient with a

detectable viral load, a provider might state, "I know it is difficult to take medicine every day. Most people miss doses at least sometimes. Thinking about the last 2 weeks, how many times have you missed doses? Please give me a rough estimate so I can help you take the best care of yourself." Other research supports simply asking patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale.[52,53]

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source. Because pill counts can be altered by patients, are labor intensive, and can be perceived as confrontational, they are generally not used in routine care. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices (e.g., Medication Event Monitoring System [MEMS] bottle caps and dispensing systems). However, these methods are costly and are generally reserved for research settings.

Improving Adherence to Antiretroviral Therapy

Strategies to improve adherence to ART are summarized in Table 16. Just as they support retention in care, all health care team members play integral roles in successful ART adherence programs.[51,54-56] An increasing number of interventions have proven effective in improving adherence to ART (for descriptions of the interventions, see http://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html). The many options can be customized to suit a range of needs and settings.

It is important that each new patient receives and understands basic information about HIV infection, including the goals of therapy (achieving and maintaining viral suppression, which will decrease HIV-associated complications and prevent transmission), the prescribed regimen (including dosing schedule and potential side effects), the importance of adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. Patients must also be positively motivated to initiate therapy, which can be assessed by simply asking patients if they want to start treatment for HIV infection. Clinicians should assist patients in identifying facilitating factors and potential barriers to adherence, and develop multidisciplinary plans to attempt to overcome those barriers. Processes for obtaining medications and refills should be clearly described. Transportation to pharmacy and to clinic visits should be assessed with linkage to appropriate services as needed. Plans to ensure uninterrupted access to ART via insurance, copay assistance, pharmaceutical company assistance programs, or AIDS Drug Assistance Programs (ADAP), for example, should be made and reviewed with the patient. Much of this effort to inform, motivate, and reduce barriers can be achieved by support staff, and can be accomplished concomitant with, or even after, starting therapy.[57-60] While delaying the initiation of ART is rarely indicated, some patients may not be comfortable starting treatment. Patients expressing reluctance to initiate ART should be engaged in counseling to understand and overcome barriers to ART initiation. Although homelessness, substance use, and mental health problems are associated with poorer adherence, they are not predictive enough at the individual level to warrant withholding or delaying therapy given the simplicity, potency, and tolerability of contemporary ART. Rapid ART initiation at the time of HIV diagnosis has been pursued as a strategy to increase viral load suppression and retention in care, but safety data, data on intermediate or long-term outcomes, and data from randomized controlled trials conducted in high-resource settings are currently lacking.[57-60] For more details, see Initiation of Antiretroviral Therapy.

The first principle of successful treatment is to design a plan to which the patient can commit.[61,62] It is important to consider the patient's daily schedule; tolerance of pill number, size, and frequency; and any issues affecting absorption (e.g., use of acid-reducing therapy and food requirements). With the patient's input, a medication choice and administration schedule should be tailored to his or her daily activities. Clinicians should explain to patients that their first regimen is usually the best option for a simple regimen that affords long-term treatment success. Establishing a trusting patient-provider relationship and maintaining good communication will help to improve adherence and long-term outcomes. Medication taking can also be enhanced using medication reminder aids. There is strongest evidence for text messaging, but pill box monitors, pill boxes, and alarms may also improve adherence.[63-67]

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed viral load and increases in CD4 T lymphocyte cell counts. Motivational interviewing has also been used with some success.[68-70] Other effective interventions include nurse home visits, a five-session group intervention, and couples- or family-based interventions. Interventions involving several approaches are generally more successful than single-strategy interventions, and interventions based on cognitive behavioral therapy and supporter interventions have been shown to improve viral suppression.[71] Problem-solving approaches that vary in intensity and culturally tailored approaches also are promising.[70,72,73] To maintain high levels of adherence in some patients, it is important to provide substance abuse therapy and to strengthen social support. DOT has been effective in providing ART to active drug users[74] but not to patients in a general clinic population[75] or in home-based settings with partners responsible for DOT.[76] The use of incentives or rewards to promote adherence has been studied, and they have been shown to improve adherence in one study.[19] However, the durability and feasibility of financial incentives are not known at this time, hence rewards for adherence are not generally recommended.[34,77,78]

Conclusion

Even armed with accurate information about a patient's adherence and barriers to ART and appointment adherence, clinicians often fail to engage patients in a productive conversation and instead simply tell patients to be adherent and offer warnings about what might ensue with continued poor adherence. This approach fails to acknowledge a patient's barriers to adherence, fails to provide the patient with actionable information, erodes rather than builds the patient-provider relationship, and has been demonstrated to not improve adherence.[79,80] At the same time, however, many of the interventions shown to improve adherence are difficult to implement in routine care. Nonetheless, effective lessons from this body of research can be applied to routine care to improve linkage to care, adherence to ART, and adherence to appointments. These lessons include the following:

- Regularly assess adherence to ART and appointments.
- Engage a patient who is struggling with adherence at any step on the care continuum with a constructive, collaborative, nonjudgmental, and problem-solving approach rather than reprimanding them or lecturing them on the importance of adherence.
- Elicit an individual's barriers to adherence, which may include personal barriers (e.g., substance use, housing instability, stigma, lack of transportation), clinic barriers (e.g., limited clinic hours, processes that make it more difficult to obtain prescriptions or schedule appointments), and system barriers (e.g., copays, prior approvals, processes that complicate maintaining pharmacy benefits or obtaining refills).
- Tailor approaches to improve adherence to an individual's needs and barriers, for example, by changing ART to simplify dosing or reduce side effects, finding resources to assist with copays or other out-of-pocket costs (see Table 16) to maintain an uninterrupted supply of ART and access to clinicians, or linking patients to counseling to overcome stigma, substance use, or depression.
- Place patients with apparent ART adherence problems on regimens with high genetic barriers to resistance, such as dolutegravir or boosted-darunavir regimens. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and patient preferences since the only regimen that will work is the one the patient can obtain and is willing and able to take.
- Understand that multidisciplinary approaches and time to understand and address barriers are needed in many situations, and that the clinician's role is to help the patient to understand the importance of adherence to the continuum of care and reveal any barriers to adherence, and link the patient to resources to overcome those barriers.

Table 16. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 1 of 2)

Strategies	Examples
Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team.	• Care providers, nurses, social workers, case managers, pharmacists, and medication managers.
Strengthen early linkage to care and retention in care.	• Encourage health care team participation in linkage to and retention in care. • Use ARTAS training (if available).
Evaluate patient's knowledge about HIV infection, prevention, and treatment and, based on this assessment, provide HIV-related information.	• Keeping the patient's current knowledge base in mind, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, therapeutic and prevention consequences of poor adherence, and importance of staying in HIV care.
Identify facilitators, potential barriers to adherence, and necessary medication management skills both before starting ART and on an ongoing basis.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges, including depression, mental illnesses, levels of social support, levels of alcohol consumption and current substance use, nondisclosure of HIV serostatus, and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of poor adherence). • Ask about medication-taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues, including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications, transportation problems.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage (e.g., Common Patient Assistance Program Application (CPAPA): http://bit.ly/CommonPAPForm; Pharmaceutical Company HIV Patient Assistance Programs and Cost-Sharing Assistance Programs: http://bit.ly/1XIahvN • Provide resources about stable housing, social support, transportation assistance, and income and food security.
Involve the patient in ARV regimen selection.	• Review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of poor adherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based or DTG-based ART if poor adherence is anticipated. • Consider use of STR formulations. • Assess if cost/copayment for drugs will affect adherence and access to medications.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale or self-reported assessment. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white-coat adherence" responses. • Ensure that other members of the health care team also assess and support adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or nondetectable levels of HIV viral load and increases in CD4 cell counts. • Thank patients for attending their appointments.

Table 16. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 2 of 2)

Strategies	Examples
Identify the type of and reasons for poor adherence and target ways to improve adherence.	• Failure to understand dosing instructions. • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements, polypharmacy). • Pill aversion or pill fatigue. • Adverse effects. • Inadequate understanding of drug resistance and its relationship to adherence. • Patient is unaware of appointments or appointments are not scheduled with proper patient input. • Cost-related issues (copays for medications or visits, missed work time). • Depression, drug and alcohol use, homelessness, poverty. • Stigma of taking pills or attending HIV-related appointments. • Nondisclosure of status leading to missed doses, refills, or appointments.
Select from among available effective adherence and retention interventions.	• See https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html for a summary of best practice interventions to improve linkage, retention, and adherence. • Use adherence-related tools to complement education and counseling interventions (e.g., text messaging, pill box monitors, pill boxes, alarms). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates, transportation assistance). • Use patient prescription assistance programs (see above, under "Provide needed resources"). • Use motivational interviews. • Provide outreach for patients who drop out of care • Use peer or paraprofessional treatment navigators. • Recognize positive clinical outcomes resulting from better adherence. • Arrange for DOT in persons in substance use treatment (if feasible). • Enhance clinic support and structures to promote linkage and retention (reminder calls, flexible scheduling, open access, active referrals, and improved patient satisfaction).
Systematically monitor retention in care.	• Record and follow up on missed visits.

Key to Acronyms: ART = antiretroviral therapy; ARTAS = Anti-Retroviral Treatment and Access to Services; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DOT = directly observed therapy; DTG = dolutegravir; PI/r = ritonavir-boosted protease inhibitor; STR = single tablet regimen

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Adverse Effects of Antiretroviral Agents (Last updated December 18, 2019; last reviewed December 18, 2019)

Adverse effects have been reported with all antiretroviral (ARV) drugs and, in the earlier era of combination antiretroviral therapy (ART), adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence.[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated because most clinical trials use highly specific inclusion criteria which exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, bone loss, and weight gain. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and managed. When selecting an ARV regimen, clinicians must consider potential adverse effects, as well as the individual's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of adverse effects. For example, underlying liver disease from alcohol use, coinfection with viral hepatitis, and/or liver steatosis[2,3] may increase the risk of hepatotoxicity when efavirenz (EFV) or protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Certain ARVs may exacerbate pre-existing conditions, for example, psychiatric disorders may be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[4,5]
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications, for example, when pharmacokinetic boosters such as ritonavir or cobicistat are used, or when isoniazid is used with EFV.[6]
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[7,8] EFV neuropsychiatric toxicity[6,9] and QTc prolongation,[10,11] and atazanavir (ATV)-associated hyperbilirubinemia.[12]

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. Table 17 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 3–9.

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 1 of 5)

Adverse effects for ARV drugs that are no longer commonly used in clinical practice (ddI, d4T, FPV/r, IDV, NFV, SQV/r, and TPV/r) have been removed from this table, with the exception of lipodystrophy and peripheral neuropathy associated with ddI and d4T. Because these effects may persist long after discontinuation of ddI or d4T, and patients may still present with these long-lasting toxicities, the drugs remain listed among the ARVs associated with these two effects. Refer to the product labels or to the July 10, 2019, version of the guidelines (found in the archived guidelines section of AIDS*info*) for information regarding the adverse effects associated with these older ARVs.

This table focuses on ARV-associated adverse effects that a patient may experience as a result of taking an ARV regimen. For information regarding potential adverse effects of ARVs on fetuses and newborns when certain ARVs are taken around the time of conception or during pregnancy, refer to Table 6b and to the Perinatal Guidelines.

In this table, N/A indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available. See Appendix B, Tables 3-9 for additional information listed by drug.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. **TAF:** Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	**ZDV:** Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	**RPV, EFV:** QTc prolongation	**ATV/r and LPV/r:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A	N/A
Cardiovascular Disease	**ABC:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	**Boosted DRV and LPV/r:** Associated with cardiovascular events in some cohorts	N/A	N/A

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 2 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Cholelithiasis	N/A	N/A	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A
Dyslipidemia	**ZDV > ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	**EFV:** ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-Boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL **LPV/r > DRV/r and ATV/r:** ↑ TG	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	N/A
Gastrointestinal Effects	**ZDV > Other NRTIs:** Nausea and vomiting	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) **LPV/r > DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	**IBA:** In a study of 40 people, 8% of patients reported diarrhea.
Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in Patients with HBV/HIV Coinfection or when HBV Resistance Develops:** Patients with HBV/HIV coinfection may develop severe hepatic flares. **ZDV:** Steatosis	**EFV:** Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	**All PIs**: Drug-induced hepatitis and hepatic decompensation have been reported. **ATV:** Jaundice due to indirect hyperbilirubinemia	**DTG:** Persons with HBV or HCV coinfection may be at higher risk of DTG-associated hepatotoxicity.	**MVC:** Hepatotoxicity with or without rash or HSRs reported.

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 3 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. **HSR Symptoms (in Order of Descending Frequency):** Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	**NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. **DTG:** Reported in <1% of patients in clinical development program	**MVC:** HSR reported as part of a syndrome related to hepatotoxicity.
Lactic Acidosis	**Reported with Older NRTIs, d4T, ZDV, and ddI**, but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A
Lipodystrophy	**Lipoatrophy:** Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, TAF or TDF.	**Lipohypertrophy:** Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated Creatine Phosphokinase	**ZDV:** Myopathy	N/A	N/A	**RAL and DTG:** ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 4 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Nervous System/ Psychiatric Effects	**History of Exposure to ddI, ddC, or d4T:** Peripheral neuropathy (can be irreversible)	**Neuropsychiatric Events:** EFV > RPV, DOR, ETR **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. **RPV:** Depression, suicidality, sleep disturbances **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm	N/A	**All INSTIs:** Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	**FTC:** Hyperpigmentation	All NNRTIs	ATV, DRV, and LPV/r	All INSTIs	MVC, IBA
Renal Effects/ Urolithiasis	**TDF:** ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. **TAF:** Less impact on renal biomarkers and lower rates of proteinuria than TDF.	**RPV:** Inhibits Cr secretion without reducing renal glomerular function.	**ATV and LPV/r:** Associated with increased risk of chronic kidney disease in a large cohort study. **ATV:** Stone or crystal formation. Adequate hydration may reduce risk. **COBI (as a Boosting Agent for DRV or ATV):** Inhibits Cr secretion without reducing renal glomerular function.	**DTG, COBI (as a Boosting Agent for EVG), and BIC:** Inhibits Cr secretion without reducing renal glomerular function	**IBA:** SCr abnormalities ≥Grade 3 reported in 10% of trial participants.

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 5 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Stevens-Johnson Syndrome/ Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV	Some reported cases for DRV, LPV/r, and ATV	RAL	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF, and greater with DOR than EFV.			INSTI > other ARV drug classes	N/A

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Switching Antiretroviral Drugs Due to Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching a patient from an effective ARV agent or regimen to a new agent or regimen must be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that drug resistant viruses previously acquired or selected, even those not detected by past genotypic resistance testing, are archived in HIV reservoirs. The resistant virus, even if absent from subsequent resistance test results, may reappear under selective drug pressure. See Optimizing Antiretroviral Therapy section for further discussion. It is critical that providers review the following information before implementing any treatment switch:

- The patient's medical and complete ARV history, including prior virologic responses to ART,

- All previous drug resistance test results,
- Viral tropism (if maraviroc [MVC] is being considered),
- HLA-B*5701 status (if ABC is being considered),
- Comorbidities,
- The patient's pregnancy status, ability to use effective contraceptives, and desire for pregnancy
- Hepatitis B virus (HBV) status. Patients with evidence of chronic HBV infection should not discontinue ARVs active against HBV (e.g., TDF, tenofovir alafenamide, lamivudine, emtricitabine). If discontinuation is necessary due to adverse effects, consult the HBV/HIV Coinfection section for guidance,
- Adherence history,
- Prior intolerances to any ARVs, and
- Concomitant medications and supplements, considering any potential drug interactions with ARVs.

A patient's willingness to accept new food requirements or dosing schedule must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient's HIV viral load should also be monitored to assure continued viral suppression.

Table 18 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in an effective ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment.

Table 18. Antiretroviral Therapy-Associated Adverse Effects That Can Be Managed with Substitution of Alternative Antiretroviral Agents (page 1 of 3)

This table focuses on ARV-associated adverse effects that patients may experience as a result of a current ARV regimen. For information regarding ARV choices to use in individuals of childbearing potential and during pregnancy to avoid potential ARV adverse effects on fetuses and newborns refer to Table 6b and to the Perinatal Guidelines.

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	TAF or ABC[b] NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	Regimen not including ZDV	ZDV has been associated with neutropenia and macrocytic anemia.
Calculi Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	This switch should be made if ATV is the presumed cause of the calculi.
Cardiac QTc Interval Prolongation	EFV, RPV	Boosted ATV or DRV, DOR, or INSTI-based regimen	High EFV and RPV exposures may cause QT prolongation. Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF or TAF	ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.
	RTV- or COBI-boosted PI regimens, EFV	RAL, DTG, BIC, RPV, or DOR	If lipids are a concern, see Dyslipidemia below. Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted EFV-based regimens	BIC, DTG, RAL, DOR, or RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	Boosted ATV or DRV, INSTI, NNRTI	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient and do not warrant ARV substitution unless they are persistent and intolerable.
	Other RTV- or COBI-boosted regimens	BIC, DTG, RAL, or NNRTI	In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC.

Table 18. Antiretroviral Therapy-Associated Adverse Effects That Can Be Managed with Substitution of Alternative Antiretroviral Agents (page 2 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Hypersensitivity Reaction	ABC	Any appropriate ABC-sparing regimen	Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status.
	EFV, ETR, NVP, RPV	Non-NNRTI ART	Risk of HSR with NVP is higher for women and those with high CD4 counts.
	DTG, RAL	Non-INSTI ART	Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases.
	MVC	Suitable alternative ART	
Insulin Resistance	LPV/r	INSTI, NNRTI	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r on insulin resistance. However, traditional risk factors for insulin resistance may be stronger risk factors than the use of any PI.
Jaundice and Icterus	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.
Lipoatrophy	Peripheral lipoatrophy (loss of subcutaneous fat of the limbs, face, and buttocks) is associated with prior thymidine analog (d4T and ZDV) use. Despite switching from these ARVs, fat recovery remains slow (may take years) and incomplete.		
Lipohypertrophy	Accumulation of visceral, truncal, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse lipohypertrophy.		
Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression, ataxia, encephalopathy	EFV, RPV	DOR, ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug, but in some patients, ataxia or encephalopathy may appear months to years after EFV-initiation. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.
Rash	NNRTIs (especially NVP and EFV)	PI- or INSTI-based regimen	Mild rashes that develop after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.
	DRV/c, DRV/r	ATV/c, ATV/r, or another drug class (e.g., INSTI)	Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] TAF (for patients with CrCl >30 mL/min, unless on chronic hemodialysis), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate.	TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting.
	ATV/c, ATV/r, LPV/r	BIC, DTG, EVG/c/TAF/FTC, RAL, boosted DRV, or NNRTI	COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by >0.4 mg/dL.

Table 18. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agents (page 3 of 3)

[a] In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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Cost Considerations and Antiretroviral Therapy (Last updated December 18, 2019; last reviewed December 18, 2019)

The clinical benefits, public health impact, and cost-effectiveness of HIV treatment are well established since the advent of combination antiretroviral therapy (ART); as a result, expanded use of ART is one of the four pillars of the "Ending the HIV Epidemic: A Plan for America" initiative.[1-6] HIV treatment with ART is costly. A 2015 study using 2012 health care expenditure data estimated that the discounted lifetime medical costs for an individual who acquires HIV at age 35 years is $326,500 ($597,300, undiscounted), with 60% of the costs attributable to ART.[7] The estimated total direct expenditures for HIV/AIDS care and treatment between 2002 and 2011 was $10.7 billion, which is 800% to 900% higher than similar expenditures for other chronic conditions.[8] Total annual undiscounted spending on antiretroviral (ARV) drugs has more than doubled since 2010, reaching $22.5 billion in 2018.[9,10] Consequently, ART was among the top five therapeutic classes in non-discounted spending on medicine in 2018, after medications for diabetes and autoimmune diseases, cancer drugs, and respiratory agents.[10]

These guidelines first included an ARV cost table in 2012.[11] Since that time, the overall cost of brand-name, first-line ART regimens has increased more than 30%. The cost of ART, especially costs to the patient, should be one of the many considerations in regimen selection because such expenditures may directly impact adherence. Overall costs to the health care system, to insurers, and to society are also important, especially given the increasing number of people who require lifelong ART and rising drug costs.

Cost Sharing in the United States

Prescription drug pricing in the United States involves complex systems with varying requirements for mandatory and voluntary discounts, rebates, and reimbursement rates, and much of the pricing information is confidential. Prices can vary depending on the state, purchaser, the type of public or private insurance coverage in use, and the number of generic competitors to branded drugs (see Table 19b). Therefore, providers may find it difficult to navigate payer cost-containment practices, including formulary restrictions, prior authorization requirements, and patient cost-sharing arrangements, such as copayments (a fixed dollar amount per prescription), co-insurance (a fixed percentage of the prescription cost), and insurance deductible payments.

Out-of-pocket costs for patients can be prohibitive, creating a barrier to the initiation and continuation of ART. Cost sharing results in higher rates of patients not initiating ART and prescription abandonment at the pharmacy, decreased adherence, more frequent drug discontinuation, and increased use of the medical system among patients with chronic diseases.[12-17] Conversely, reducing patient out-of-pocket costs (e.g., through manufacturer copayment-assistance programs or by prescribing generic drugs instead of more costly brand-name products) has been associated with improved adherence.[18] Given the clear association between out-of-pocket costs and the ability to pay for and adhere to medications, clinicians should minimize patients' out-of-pocket drug-related expenses whenever possible. However, many of the cost-sharing arrangements that determine out-of-pocket costs are not transparent to clinicians or patients at the time decisions on ART are made.

Maximum allowable copayments on prescription drugs covered by Medicaid can vary by family income but are usually nominal. For commercial insurers, cost sharing is generally subject to maximum payment rules under the Affordable Care Act. Manufacturer cost-sharing assistance programs are available for most brand-name ARV products but may be restricted by pharmacy and by state. Manufacturer copay assistance may also be subject to copay accumulator programs implemented by insurers' pharmacy benefit managers, whereby manufacturer payments do not count toward a patient's deductible or out-of-pocket maximum.

Medicare Part D plan cost sharing can include deductibles and copayments or coinsurance, including out-of-pocket payments of up to 25% on prescription drugs during the annual coverage gap phase ("donut hole") and up to 5% during the annual catastrophic coverage phase.[19] Low-income beneficiaries may qualify for subsidies to defray cost-sharing payments. Manufacturer copay assistance programs may not be applied toward Medicare plan cost sharing, but assistance from independent foundations (e.g., Patient Access

Network Foundation, Patient Advocate Foundation) may provide cost-sharing support if financial eligibility criteria are met.

AIDS Drug Assistance Programs (ADAPs), through the Ryan White HIV/AIDS Program, make ARVs and other prescription drugs accessible to people with HIV who are underinsured and have limited financial resources. Further, many ADAPs provide premium and cost-sharing assistance to eligible clients covered by Medicaid, commercial insurance plans, or Medicare Part D plans.

Generic Antiretrovirals and Multi-Tablet Regimens

In 2017, savings to the U.S. health care system generated by the use of generic drugs and biosimilar products totaled $265 billion, including $40.6 billion and $82.7 billion in savings to Medicaid and Medicare, respectively.[20]

With substantial improvements in the long-term safety and effectiveness of contemporary ART, a number of regimens and regimen components in Table 6a remain listed beyond their patent protection date and are or will be available as lower-cost generic options. In one study, the savings associated with a transition to a hypothetical lower-cost generic ART could potentially help cover the 20-year, $480 billion projected costs to reach national treatment targets.[5]

Some research informs the cost impact of use of specific generic ARV regimens or regimen components. In a cost-effectiveness analysis conducted before the availability of integrase strand transfer inhibitors (INSTIs), the use of generic efavirenz (EFV) had an estimated saving of nearly $1 billion, and a regimen with generic EFV was very cost-effective.[2] A more recent study describes a 25% reduction in both the wholesale acquisition cost and federal supply schedule cost associated with switching from branded coformulated dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) to branded DTG plus generic ABC and generic 3TC.[2,21]

A number of generic options of ARV regimen components included in Table 6a are commercially available. Generic tenofovir disoproxil fumarate (TDF), generic 3TC, or a lower-cost brand-name coformulation of TDF and 3TC may be combined with DTG or raltegravir. Generic versions of ABC, 3TC, and ABC/3TC are also available for use with DTG. Generic versions of EFV, atazanavir, and ritonavir are available for use, along with lower-cost brand-name coformulations of EFV (either 600 mg or 400 mg) with TDF and 3TC. TDF and 3TC have also been coformulated with doravirine, with a list price that is moderately lower than other single-tablet regimens containing only proprietary ARVs (Table 19b).

There is keen interest in assessing the economic value of using newer, more expensive drugs that have only incremental clinical benefits when compared with older, less expensive drugs. One study investigated the cost-effectiveness of TDF- versus TAF-based regimens.[22] The study demonstrated that the similar efficacy—but slightly improved toxicity profile—of the TAF-based regimens would justify a $1,000 higher annual premium for the TAF-based regimens. The study further highlighted that once generic TDF becomes available at much lower costs, TAF-based regimens will only remain cost-effective if their annual cost is no more than $1,000 above that of generically available TDF-based regimen. (Generic TDF was approved in 2018.)

The use of DTG plus generic 3TC for initial therapy has been evaluated in a cost-containment analysis. One study projected that if just 50% of patients with newly diagnosed HIV initiated a two-pill regimen consisting of branded DTG plus generic 3TC, the cost savings would reach $550 to $800 million over a 5-year period.[23] If 25% of patients with sustained viral suppression switched to branded DTG plus generic 3TC maintenance therapy, cost savings were projected to exceed $3 billion in just 5 years.[23]

Because all commercially available single-tablet regimens (STRs) (including those containing ARV components that are no longer patent protected) are branded products, use of generics in the United States may necessitate modest increases in pill burden, but without changes in drug frequency. One study of Medicare Part D spending, which included expenditures for one ARV fixed-dose combination tablet (ABC/3TC), demonstrated that splitting up brand-name coformulated products into their generic components could have saved Medicare an

estimated $2.7 billion from 2011 through 2016, and highlighted this approach as a critical cost-containment measure.[24] However, to the extent that pill burden, rather than drug frequency, results in reduced adherence, generic ART could lead to decreased costs but at the potential expense of worsening virologic suppression rates and poorer clinical outcomes.[14,15] Additionally, a benefit of STRs is that there is no risk that one drug in the regimen will be temporarily or permanently discontinued due to prescribing error, unsynchronized refill schedules, or prohibitive out-of-pocket costs. Data to support or refute the superiority of once-daily STRs versus once-daily multi-tablet regimens, particularly based on virologic outcomes and especially following viral suppression, remain limited. One large observational cohort study demonstrated a small but statistically significant virologic efficacy benefit associated with STRs.[25] In this study, the time to treatment discontinuation was shorter for non-STRs than for STR once-daily regimens; however, this difference disappeared when modifications for regimen simplification were included in the analysis.

Importantly, when the costs of brand-name drug products and generic ARV drugs are compared, savings associated with generic ARV drugs may vary when branded drugs are subject to discounts or rebates across public and private payer systems. Although generic drug products may be associated with societal cost savings and, specifically, savings for public payers, commercial insurers, and people with HIV with significant out-of-pocket pharmacy expenses, manufacturer copay assistance is generally not available to commercially insured individuals. In cases where manufacturer copay assistance may be available for a brand-name ARV product but not for an equivalent generic ARV product, the generic drug prescription paradoxically may result in higher out-of-pocket costs.

Laboratory Services

In the context of lifelong ART, the amount of money to be saved by performing infrequent or one-time only tests (e.g. genotypes or serologies), even expensive tests, is modest. Even so, judicious use of laboratory testing, without compromising patient care, can still be an important way to reduce costs. For patients with deductibles for laboratory tests, decreasing the use of tests with limited clinical value could reduce patient costs and improve adherence to a care plan. Several studies have examined the value of laboratory services in HIV care. One cost analysis study suggested that there may be no clinical benefit to continuing CD4 monitoring in patients with suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[16] In the United States, reducing biannual CD4 monitoring to annual monitoring could save approximately $10 million per year.[26] Another study examined more than 250 patients with HIV who were hospitalized over 500 times in a 6-month period. The inpatient chart review demonstrated that 45% of ordered laboratory tests were not indicated—including hepatitis serologies, other serologies, and cytomegalovirus polymerase chain reaction. During this 6-month period at this single site, the estimated cost of excess and inappropriate laboratory testing totaled $14,000 to $92,000.[27]

Cost-effectiveness analyses from 2001 and 2005 demonstrated the value of genotype resistance testing in ART-experienced and ART-naive patients and supported the guidelines' recommendation for performing resistance testing before ART initiation and at time of virologic failure.[28,29] More recent cost-effectiveness analyses have revisited the value of baseline, pre-treatment genotype testing in the setting of INSTI plus two-nucleoside reverse transcriptase inhibitors (NRTIs) regimens. One modeling study suggested that INSTI-specific genotype testing before initiation of a DTG plus two NRTIs regimen was not cost-effective and may lead to underutilization of INSTIs; the results highlighted that some patients with INSTI-resistance would still become virologically suppressed on a DTG-based regimen.[30] A second modeling study found that standard (NRTI, non-nucleoside reverse transcriptase inhibitor, protease inhibitor) genotype testing before ART initiation was also not cost-effective because it may have little impact on outcomes given the use of an INSTI plus 2 NRTIs in first-line treatment.[31] Both of these modeling studies only assessed the use of genotype testing for decision making for initial ART, and presumed such testing would be available for use at the time of first-line failure. The results of these modeling studies suggest that additional clinical research is needed to define the role of genotypic resistance testing before initiation of an INSTI plus 2-NRTI regimen.

Importantly, these modelling data do not apply to two-drug ARV regimens, which are increasingly being prescribed in clinical practice. It should be noted that the Panel continues to recommend baseline testing for clinically relevant protease and reverse transcriptase mutations (see Drug-Resistance Testing section).

Conclusion

Ideally, costs should not drive clinical care, yet they are a factor in contemporary health care. Because regimen costs may impact patients' ability to afford and adhere to therapy, understanding ART-related costs in the United States is increasingly important. Providers play a key role in ensuring optimal care while working to both: 1) minimize costs for ARV drugs and avoid or minimize unnecessary laboratory monitoring and 2) retain excellent clinical outcomes in an environment of cost-containment strategies, including formulary restrictions, utilization management (e.g., prior authorization), and cost sharing. Providers should therefore remain informed of current insurance and payment structures, ART costs (see Table 19b below for estimates of drugs' average prices), out-of-pocket expenditure requirements, and available generic ARV options. Providers should work with patients and their pharmacists, social workers, case managers, and/or peer navigators to understand their patients' medication benefits and any potential financial barriers to prescription fulfillment. This information will help providers identify treatment options that are safe, effective, and affordable. Engaging with patients about any cost constraints during the process of regimen selection will likely facilitate adherence. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company assistance programs for patients who qualify) and refer patients to such assistance if needed.

Table 19a. Insurance and Health Program Prescription Drug Pricing and Access (page 1 of 2)

Insurance/Health Program	Prescription Drug Pricing and Access
Medicaid	Drug manufacturers must participate in MDRP for their drugs to be covered by Medicaid and under Medicare Part B. Manufacturers are required to pay Medicaid programs a rebate of at least 23.1% of the average price paid to manufacturers by wholesalers (AMP) for most brand-name drugs sold to retail pharmacies (13% for generics). Manufacturers pay additional rebates if this confidential AMP increases faster than the CPI-U rate of inflation. States are permitted to require "nominal" cost-sharing for medical and pharmacy benefits for some beneficiaries though many elect not to do so. States can obtain a waiver to allow them to apply higher cost-sharing.
Medicare	ARVs are one of six "protected drug classes" under Medicare Part D. Part D plans must provide access to all, or substantially all, FDA-approved ARVs. Part D plan sponsors, or PBMs on their behalf, negotiate rebates on outpatient drugs with manufacturers; the extent of rebating is unclear. Most physician-administered drugs and biologics are covered under Medicare Part B at a set cost: ASP plus 6%. This pricing mechanism controls spending by narrowing the spread between what is actually paid for the drug and what is actually billed to Medicare. Premiums and cost-sharing payments may be significant for both services and prescription drugs; there is no cap on out-of-pocket spending under Part A (hospital care) and Part B. Some subsidies and supplemental coverage are offered for low-income beneficiaries. Manufacturer copay assistance programs cannot be applied to Part B or Part D cost sharing; cost sharing support is available from ADAPs, foundations, and other sources, based on financial eligibility criteria.
Commercial Insurance	Private insurance plans, or PBMs on their behalf, negotiate rebates on inpatient and outpatient drugs with manufacturers; the extent of rebating is unclear. Formulary restrictions and utilization management (prior authorization, step therapy, higher cost sharing) are possible as cost-containment measures. Cost sharing can be highly variable. Manufacturer copay assistance programs can be applied in most cases but may not count toward annual Affordable Care Act cost sharing limits; cost sharing support is also available from ADAPs, foundations, and other sources based on financial eligibility criteria.

Table 19a. Insurance and Health Program Prescription Drug Pricing and Access (page 2 of 2)

Insurance/Health Program	Prescription Drug Pricing and Access
ADAPs	Significant discounting on most ARVs negotiated by the ADAP Crisis Task Force is allowed under the 340B Drug Pricing Program. There is usually no cost sharing for ADAP clients who are uninsured. ADAP can assist with commercial or public insurance out-of-pocket costs.
Veterans Affairs	The FCP is the maximum price manufacturers may charge the four largest federal purchasers of pharmaceuticals (the "Big Four"): The Department of Veterans Affairs, the Department of Defense, the Public Health Service (including the Indian Health Service), and the Coast Guard. The FCP of a drug includes a 24% discount on a drug's average price paid by non-federal purchasers. Additional discounts may be applied if non-federal purchase prices increase faster than the CPI-U inflation rate. Big Four prices may be 40% to 50% below list prices. VA may negotiate further price reductions. Prescription drug cost sharing is generally nominal; medications are not withheld from those who cannot afford cost sharing expenses.
Community Health Centers	Many community health centers are enrolled in the 340B Drug Pricing Program, which allows for discounted drug purchasing using the MDRP formula. Discounts start at 23.1% off AMP, with additional discounts if the AMP increases faster than the CPI-U rate of inflation. Cost-sharing in community health centers is first driven by payer source. For clients who are uninsured, cost-sharing, if required, is typically based on a sliding fee scale.

Key: ADAP = AIDS Drug Assistance Programs; AMP = average manufacturer price; ARV = antiretroviral; ASP = average sales price; CPI-U = consumer price index-urban; FCP = Federal Ceiling Price; FDA = Food and Drug Administration; MDRP = Medicaid Drug Rebate Program; PBM = pharmacy benefits manager; VA = Veterans Affairs

Table 19b. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 5)

Table 19b includes three benchmark prices, rounded to the nearest dollar, for commonly used ARV drugs[a] as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact patients' pharmacies or payers regarding actual prices, comparative cost savings, formulary restrictions, and patient cost-sharing requirements.

Wholesale acquisition cost (WAC) is the list price published by manufacturers for prescription drugs or biologics sold to wholesalers. The WAC price approximates what retail pharmacies pay wholesalers for single-source (e.g., brand-name) drugs. There is a range of WAC prices for generic ARV drugs, as these are multiple-source products with variable list prices. With increasing competition, actual transactional prices of generic drugs among wholesalers and pharmacies decrease substantially. **Average wholesale price (AWP)** has historically been used as the basis for setting public (e.g., Medicaid) and private (e.g., commercial insurer) reimbursement rates for pharmacies. Neither WAC nor AWP include variable price concessions along supply and payment chains, including discounts and rebates to wholesalers, pharmacies, federal purchasers (e.g., the Veterans' Administration), pharmacy benefit managers (PBMs), commercial insurers, Medicaid, 340B pharmacies, and AIDS Drug Assistance Programs. The availability of these discounts and rebates depends on product demand, market competition, and WAC price increases set by manufacturers. Maximum prices are assigned to generic products with three or more therapeutically and pharmaceutically equivalent products, as determined by the Food and Drug Administration. This federally established price is the **federal upper limit (FUL)**. Federal Medicaid will reimburse state Medicaid programs up to this limit for multiple-source drugs (plus the dispensing fee); commercial insurers set their own reimbursement upper limits with pharmacies. Whereas WACs and AWPs are generally set annually, FULs are adjusted on a monthly basis, particularly for multiple-source drugs with fluctuating pharmacy acquisition costs. In the table below, the FUL for a drug is described as "pending" if a generic drug currently lacks the competition required to trigger a FUL.

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
NRTIs					
Abacavir					
• Generic	300 mg tablet	60 tablets	$150 to $482	$502 to $603	$43
• Ziagen	300 mg tablet	60 tablets	$559	$670	
Emtricitabine					
• Emtriva	200 mg capsule	30 capsules	$537	$644	N/A
Lamivudine					
• Generic	300 mg tablet	30 tablets	$75 to $343	$324 to $430	$51
• Epivir	300 mg tablet	30 tablets	$416	$499	
Tenofovir Disoproxil Fumarate					
• Generic	300 mg tablet	30 tablets	$27 to $163	$110 to $1,216	$203
• Viread	300 mg tablet	30 tablets	$1,196	$1,435	

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
NRTIs, continued					
Zidovudine					
• Generic	300 mg tablet	60 tablets	$36 to $54	$54 to $365	$13
NRTI Combination Products					
Abacavir/Lamivudine					
• Generic	600 mg/300 mg tablet	30 tablets	$185 to $1,116	$1,393 to $1,550	$182
• Epzicom	600 mg/300 mg tablet	30 tablets	$1,292	$1,550	
Tenofovir Alafenamide/Emtricitabine					
• Descovy	25 mg/200 mg tablet	30 tablets	$1,758	$2,109	N/A
Tenofovir Disoproxil Fumarate/Emtricitabine					
• Truvada	300 mg/200 mg tablet	30 tablets	$1,676	$2,011	N/A
Tenofovir Disoproxil Fumarate/Lamivudine					
• Cimduo	300 mg/300 mg tablet	30 tablets	$1,005	$1,207	N/A
• Temixys	300 mg/300 mg tablet	30 tablets	$850	$1,020	N/A
Zidovudine/Lamivudine					
• Generic	300 mg/150 mg tablet	60 tablets	$134 to $578	$878 to $932	$123
• Combivir	300 mg/150 mg tablet	60 tablets	$901	$1,082	
Abacavir Sulfate/Zidovudine/Lamivudine					
• Generic	300 mg/300 mg/150 mg tablet	60 tablets	$1,391	$1,738	Pending
• Trizivir	300 mg/300 mg/150 mg tablet	60 tablets	$1,610	$1,932	
NNRTIs					
Efavirenz					
• Generic	600 mg tablet	30 tablets	$894 to $980	$1,073 to $1,117	$768
• Sustiva	600 mg tablet	30 tablets	$981	$1,177	
Doravirine					
• Pifeltro	100 mg tablet	30 tablets	$1,380	$1,656	N/A
Etravirine					
• Intelence	200 mg tablet	60 tablets	$1,366	$1,628	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
NNRTIs, continued					
Nevirapine					
• Generic	200 mg tablet	60 tablets	$10 to $45	$648 to $651	$65
• Viramune	200 mg tablet	60 tablets	$906	$1,087	
• Generic XR	400 mg tablet	30 tablets	$135 to $565	$595 to $706	$392
• Viramune XR	400 mg tablet	30 tablets	$840	$1,008	
Rilpivirine					
• Edurant	25 mg tablet	30 tablets	$1,115	$1,338	N/A
PIs					
Atazanavir					
• Generic	200 mg capsule	60 capsules	$445 to $1,264	$1,517 to $1,668	$1,405
• Reyataz	200 mg capsule	60 capsules	$1,463	$1,756	
• Generic	300 mg capsule	30 capsules	$445 to $1,252	$1,502 to $1,652	$1,032
• Reyataz	300 mg capsule	30 capsules	$1,449	$1,739	
Atazanavir/Cobicistat					
• Evotaz	300/150 mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
• Prezista	600 mg tablet	60 tablets	$1,690	$2,028	N/A
• Prezista	800 mg tablet	30 tablets	$1,690	$2,028	N/A
• Prezista	100 mg/mL suspension	200 mL	$939	$1,126	N/A
Darunavir/Cobicistat					
• Prezcobix	800 mg/150 mg tablet	30 tablets	$1,931	$2,317	N/A
Lopinavir/Ritonavir					
• Kaletra	200 mg/50 mg tablet	120 tablets	$1,024	$1,229	N/A
Tipranavir					
• Aptivus	250 mg capsule	120 capsules	$1,673	$2,008	N/A
INSTIs					
Dolutegravir					
• Tivicay	50 mg tablet	30 tablets	$1,740	$2,089	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
INSTIs, continued					
• Tivicay	50 mg tablet	60 tablets	$3,480	$4,178	N/A
Raltegravir					
• Isentress	400 mg tablet	60 tablets	$1,574	$1,889	N/A
• Isentress HD	600 mg tablet	60 tablets	$1,574	$1,889	N/A
Fusion Inhibitor					
Enfuvirtide					
• Fuzeon	90 mg injection kit	60 doses (1 kit)	$3,586	$4,303	N/A
CCR5 Antagonist					
Maraviroc					
• Selzentry	150 mg tablet	60 tablets	$1,556	$1,867	N/A
• Selzentry	300 mg tablet	60 tablets	$1,556	$1,867	N/A
• Selzentry	300 mg tablet	120 tablets	$3,112	$3,734	N/A
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk					
• Trogarzo	200 mg vial	8 vials	$9,080	$10,896	N/A
Coformulated Combination Products as Single-Tablet Regimens					
Bictegravir/Tenofovir Alafenamide/Emtricitabine					
• Biktarvy	50 mg/25 mg/200 mg tablet	30 tablets	$3,089	$3,707	N/A
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Symtuza	800 mg/150 mg/10 mg/200 mg tablet	30 tablets	$3,722	$4,466	N/A
Dolutegravir/Abacavir/Lamivudine					
• Triumeq	50 mg/600 mg/300 mg tablet	30 tablets	$2,889	$3,467	N/A
Dolutegravir/Lamivudine					
• Dovato	50 mg/300 mg tablet	30 tablets	$2,295	$2,754	N/A
Dolutegravir/Rilpivirine					
• Juluca	50 mg/25 mg tablet	30 tablets	$2,707	$3,249	N/A
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine					
• Delstrigo	100 mg/300 mg/300 mg tablet	30 tablets	$2,100	$2,520	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
Coformulated Combination Products as Single-Tablet Regimens, continued					
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Atripla	600 mg/300 mg/200 mg tablet	30 tablets	$2,858	$3,429	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine					
• Symfi	600 mg/300 mg/150 mg tablet	30 tablets	$1,634	$1,961	N/A
• Symfi Lo	400 mg/300 mg/150 mg tablet	30 tablets	$1,634	$1,961	N/A
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Genvoya	150 mg/150 mg/10 mg/200 mg tablet	30 tablets	$3,090	$3,708	N/A
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Stribild	150 mg/150 mg/300 mg/200 mg tablet	30 tablets	$3,241	$3,889	N/A
Rilpivirine/Tenofovir Alafenamide/Emtricitabine					
• Odefsey	25 mg/25 mg/200 mg tablet	30 tablets	$2,812	$3,375	N/A
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Complera	25 mg/300 mg/200 mg tablet	30 tablets	$2,812	$3,375	N/A
PK Enhancers (Boosters)					
Cobicistat					
• Tybost	150 mg tablet	30 tablets	$230	$277	N/A
Ritonavir					
• Generic	100 mg tablet	30 tablets	$80 to $222	$278	$78
• Norvir	100 mg tablet	30 tablets	$257	$309	

[a] The following less commonly used ARV drugs are not included in this table: DLV, ddI, FPV, IDV, NFV, SQV, and d4T.

[b] Source: Micromedex Red Book [database]. IBM Watson Health. 2019. Available at: https://www.micromedexsolutions.com

[c] Source: Federal Upper Limits–October 2019 [database]. Medicare & Medicaid Services. 2019. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html.

Key: ARV = antiretroviral; AWP = average wholesale price; CD4 = CD4 T lymphocyte; d4t = stavudine; ddI = didanosine; DLV = delavirdine; FPV = fosamprenavir; FUL = federal upper limit; HD = high dose; IDV = indinavir; INSTI = integrase strand transfer inhibitor; N/A = not applicable; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; SQV = saquinavir; WAC = wholesale acquisition cost; XR = extended release

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Drug-Drug Interactions (Last updated December 18, 2019; last reviewed December 18, 2019)

Pharmacokinetic (PK) drug-drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug-drug interactions—both those affecting ARVs and those affecting concomitant drugs. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. Tables 21a through 22b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modification of ARVs or concomitant medicines or for alternative therapy.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common drug interaction mechanisms are described below and listed for individual ARV drugs in Table 20.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents, such as proton pump inhibitors, H2 antagonists, or antacids, can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir and rilpivirine).
- Products that contain polyvalent cations, such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium, can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 (CYP) 3A4 or efflux transporter P-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions:

- The CYP450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), the CCR5 antagonist maraviroc, and the INSTI elvitegravir. CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTI raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PKs of these INSTIs.

- The INSTIs bictegravir and dolutegravir have mixed metabolic pathways, including both CYP3A4 and UGT1A1. Drugs that induce or inhibit these enzymes may have variable impact on the PKs of these INSTIs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir (RTV) and cobicistat (COBI). Both drugs are potent inhibitors of the CYP3A4 enzyme, and thus, when coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters. The influence of drug transporters on drug-drug interactions is complex, and the clinical significance of these interactions is unclear but is under investigation. Further understanding of these pathways, and the clinical significance of this drug interaction mechanism is needed.

Role of Therapeutic Drug Monitoring in Managing Drug-Drug Interactions

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important drug-drug interaction, the first step is to assess whether other, equally effective treatment options can be used to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Drug concentration assays for some ARV drugs are commercially available; however, results reporting may take 1 week or longer. When interpreting assay results, clinicians should consider the patient's medication adherence, the timing of last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, TDM must be repeated after the dose-adjusted drug reaches steady state to assure appropriate dosing.

TDM information should not be used alone; it must be considered in conjunction with other clinical information, including virologic response and signs and symptoms of drug toxicities, to assure safe and effective therapy.

Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 2)

PK interactions may occur during absorption, metabolism, or elimination of the ARV drug and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV drugs described in the row and may not be reflective of complete ARV regimens. The older PIs FPV, IDV, NFV, and SQV are not commonly used in clinical practice and are **not** included in this table. Please refer to the FDA product labels for FPV, IDV, NFV, and SQV for information regarding drug interactions with these PIs.

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
INSTIs							
BIC	N/A	Concentration decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4	N/A	N/A	Substrate
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate
EVG/c	N/A		Inhibitor	3A4	3A4, 2D6	2C9	Substrate
RAL	N/A		N/A	N/A	N/A	N/A	Substrate
PIs							
ATV	Concentration decreased	N/A	Substrate, Inducer, Inhibitor	3A4	3A4, 2C8	N/A	Inhibitor
ATV/c	Concentration decreased	N/A	Substrate, Inhibitor	3A4	3A4, 2D6, 2C8	N/A	Inhibitor
ATV/r	Concentration decreased	N/A	Substrate, Inhibitor	3A4, 2D6	3A4, 2D6, 2C8	1A2, 2B6, 2C8, 2C9, 2C19	**ATV:** Inhibitor **RTV:** Inducer
DRV/c	N/A	N/A	Substrate, effect on P-gp unknown	3A4	3A4, 2D6	N/A	No data
DRV/r	N/A	N/A	Substrate, effect on P-gp unknown	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
LPV/r	N/A	N/A	Substrate	3A4, 2D6	3A4	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
TPV/r	N/A	N/A	Substrate, Inducer	3A4, 2D6	3A4, 2D6	No data	Inducer
NNRTIs							
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A

Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
NNRTIs, continued							
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A
RPV	Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A
NRTIs							
ABC	N/A	N/A	N/A	N/A	N/A	N/A	Substrate
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
ZDV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CCR5 Antagonist							
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
Fusion Inhibitor							
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; Ca = calcium; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FPV = fosamprenavir; FTC = emtricitabine; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; P-gp = P-glycoprotein; PK = pharmacokinetic; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate glucuronosyltransferase; ZDV = zidovudine; Zn = zinc

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 19)

This table provides information on the known or predicted interactions between PIs and non-ARV drugs. When information is available, interactions for boosted ATV (with either RTV or COBI) and unboosted ATV are listed separately. The term "All PIs" refers to both unboosted ATV and PIs boosted with either RTV or COBI, except for FPV, IDV, NFV, and SQV. For information regarding interactions between PIs and other ARV drugs, including dosing recommendations, refer to Tables 21c, 22a, and 22b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Note: FPV, IDV, NFV, and SQV are no longer commonly used in clinical practice and are **not** included in this table. Please refer to the FDA product labels for FPV, IDV, NFV, and SQV for information regarding drug interactions between these PIs and concomitant medications.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	**When Given Simultaneously:** • ↓ ATV expected	Administer ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.
	TPV/r	TPV AUC ↓ 27%	Administer TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	**When Given Simultaneously with Famotidine:** • ATV AUC ↓ 41% **When Given 2 Hours Before and ≥10 Hours After H2RA:** • ↔ ATV	A single dose of H2RA should not exceed a dose equivalent to famotidine 20 mg, and the total daily dose should not exceed a dose equivalent to famotidine 20 mg twice daily in PI-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2RA. **Do not coadminister** unboosted ATV plus H2RA in PI-experienced patients.
	ATV/c, ATV/r	↓ ATV expected	H2RA dose should not exceed a dose equivalent to famotidine 40 mg twice daily in ART-naive patients or famotidine 20 mg twice daily in ART-experienced patients. Give ATV 300 mg (plus COBI 150 mg **or** RTV 100 mg) simultaneously with and/or ≥10 hours after the dose of H2RA. If using TDF and H2RA in ART-experienced patients, use ATV 400 mg (plus COBI 150 mg **or** RTV 100 mg).
	DRV/c, DRV/r, LPV/r, TPV/r	**With Ranitidine:** • ↔ DRV/r ↔ PI expected	No dose adjustment needed.
Proton Pump Inhibitors	ATV (unboosted)	**With Omeprazole 40 mg:** • ATV AUC ↓ 94%	**Do not coadminister**.
	ATV/c, ATV/r	**With Omeprazole 40 mg:** • ATV AUC ↓ 76% **When Omeprazole 20 mg is Given 12 Hours before ATV/c or ATV/r:** • ATV AUC ↓ 42%	PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **Do not coadminister in PI-experienced patients.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Proton Pump Inhibitors	DRV/c, LPV/r	↔ PI expected	No dose adjustment needed.
	DRV/r	↔ DRV/r Omeprazole AUC ↓ 42%	Consider alternative ARV or acid reducer. If coadministered, monitor for omeprazole efficacy. If patient does not experience symptomatic relief, increase dose to no more than omeprazole 40 mg daily.
	TPV/r	↔ TPV/r Omeprazole AUC ↓ 70%	**Do not coadminister**.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	**Do not coadminister, unless benefits outweigh risks.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/adverse events. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	**Contraindicated.**
Antibacterials			
Antimycobacterials			
Bedaquiline	All PIs	**With LPV/r:** • Bedaquiline AUC ↑ 1.9-fold **With other PI/r, ATV/c, or DRV/c:** • ↑ bedaquiline possible	**Do not coadminister, unless benefits outweigh risks.** Monitor liver function and ECG for QTc prolongation.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Recommended dose is rifabutin 150 mg once daily. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.
	ATV/r	**Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r:** • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	**Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r:** • ↔ rifabutin AUC and metabolite AUC ↑ 881%	
	LPV/r	**Compared with Rifabutin (300 mg Daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r:** • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	TPV/r	Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%	
	PI/c	↑ rifabutin expected ↓ COBI expected	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials, continued			
Antimycobacterials, continued			
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. Increasing the COBI dose is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister**.
Macrolides			
Azithromycin	ATV (unboosted), ATV/c, ATV/r	↑ azithromycin possible	No dose adjustment needed.
	DRV/c, DRV/r, TPV/r	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	ATV (unboosted)	Clarithromycin AUC ↑ 94%	Reduce clarithromycin dose by 50% or consider alternative ARV or azithromycin. Monitor for clarithromycin-related adverse events, including QTc prolongation.
	PI/c, PI/r	DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg twice daily ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	Consider alternative ARV or azithromycin. Monitor for clarithromycin-related adverse events, including QTc prolongation. If use of clarithromycin is necessary in a patient with impaired renal function, reduce clarithromycin dose by 50% in patients with CrCl 30 to 60 mL/min. In patients with CrCl <30 mL/min, reduce clarithromycin dose by 75%.
Erythromycin	All PIs	↑ erythromycin expected ↑ PIs expected	Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. **In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily:** • Reduce apixaban dose by 50%.
Betrixaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ betrixaban expected	Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
Dabigatran	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ dabigatran expected **With COBI 150 mg Alone:** • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants, continued			
Edoxaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	ATV/c, ATV/r, LPV/r	↑ edoxaban expected	**Stroke Prevention in Nonvalvular Atrial Fibrillation Indication:** • No dose adjustment needed. **Deep Venous Thrombosis and Pulmonary Embolism Indication:** • Administer edoxaban 30 mg once daily.
	DRV/c, DRV/r, TPV/r	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
Rivaroxaban	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or anticoagulant.
	PI/c, PI/r	↑ rivaroxaban expected	**Do not coadminister**.
Warfarin	PI/c	No data	Monitor INR closely when stopping or starting PI/c or PI/r and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.
	PI/r	↓ warfarin possible	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI concentrations substantially	**Do not coadminister**.
	ATV/r, LPV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI concentrations substantially	Consider alternative ARV or anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	Carbamazepine AUC ↑ 45% ↔ DRV	Monitor anticonvulsant concentration and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Eslicarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Ethosuximide	All PIs	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	ATV (unboosted)	↔ lamotrigine	No dose adjustment needed.
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; monitor lamotrigine concentration or consider alternative ARV or anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% ↔ LPV	
	DRV/r, TPV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant concentration and adjust dose accordingly.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Oxcarbazepine	All PIs	↓ PI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentrations.
Phenobarbital	ATV (unboosted)	↓ ATV expected	**Do not coadminister**.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	↓ phenytoin possible ↓ LPV/r possible	**Do not coadminister with LPV/r once daily.** Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	PI/c	↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Phenytoin	ATV (unboosted)	↓ ATV expected	**Do not coadminister**.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant. If coadministration is necessary, consider monitoring concentrations of both drugs and assessing virologic response.
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	**Do not coadminister with LPV/r once daily.** Consider alternative anticonvulsant or monitor concentrations of both drugs and assess virologic response.
	PI/c	↓ cobicistat expected ↓ PI expected	**Contraindicated.**
Valproic Acid	All PIs	↓ or ↔ VPA possible LPV AUC ↑ 38% No data for other PIs	Monitor VPA concentrations and monitor for PI tolerability.
Antidepressants, Anxiolytics, and Antipsychotics Also see Sedative/Hypnotics section below			
Bupropion	ATV/r, DRV/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
	LPV/r	Bupropion AUC ↓ 57%	
	PI/c	↔ bupropion expected	No dose adjustment needed.
Buspirone	All PIs	↑ buspirone expected	Administer lowest dose of buspirone with caution and titrate buspirone dose based on clinical response.
Nefazodone	All PIs	↑ nefazodone expected ↑ PI possible	Monitor for nefazodone-related adverse events and PI tolerability.
Trazodone	All PIs	RTV 200 mg twice daily (for 2 days) ↑ trazodone AUC 240%	Administer lowest dose of trazodone and monitor for CNS and CV adverse events.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 6 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics, continued Also see Sedative/Hypnotics section below			
Tricyclic Antidepressants Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine	All PIs	↑ TCA expected	Administer lowest possible TCA dose and titrate based on clinical assessment and/or drug concentrations.
Selective Serotonin Reuptake Inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	All PIs except DRV/r	No data	Titrate SSRI dose using the lowest available initial or maintenance dose.
Antipsychotics			
Aripiprazole	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Brexpiprazole	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
	ATV (unboosted)	↑ brexpiprazole expected	Administer 50% of the usual brexpiprazole dose. Titrate dose based on clinical monitoring for efficacy/adverse events. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.
Cariprazine	All PIs	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving a PI:** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased. **Starting a PI in a Patient Who Is Already Receiving Cariprazine:** • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, cariprazine dose may need to be increased.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 7 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics, continued Also see Sedative/Hypnotics section below			
Antipsychotics, continued			
Iloperidone	All PIs	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lurasidone	ATV (unboosted)	↑ lurasidone expected	Consider alternative ARV or antipsychotic. If coadministration is necessary, reduce lurasidone dose by 50%.
	PI/c, PI/r	↑ lurasidone expected	**Contraindicated.**
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., clozapine, perphenazine, risperidone, thioridazine)	PI/c, PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose or adjust maintenance dose accordingly. Monitor for adverse events, including QTc prolongation.
Pimavanserin	ATV (unboosted)	No data	No data available for dose recommendation. Consider alternative ARV or antipsychotic.
	LPV/r	↑ pimavanserin expected	**Do not coadminister**, due to risk for QTc prolongation.
	All other PIs	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg once daily.
Pimozide	All PIs	↑ pimozide expected	**Contraindicated.**
Quetiapine	All PIs	↑ quetiapine expected	**Starting Quetiapine in a Patient Receiving a PI:** • Initiate quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse events. **Starting a PI in a Patient Receiving a Stable Dose of Quetiapine:** • Reduce quetiapine dose to 1/6 of the current dose. Closely monitor for quetiapine effectiveness and adverse events.
Ziprasidone	LPV/r	↑ ziprasidone expected	**Do not coadminister,** due to risk for QTc prolongation.
	All PIs except LPV/r	↑ ziprasidone expected	Monitor for ziprasidone-related adverse events.
Antifungals			
Fluconazole	TPV/r	TPV AUC ↑ 50%	Fluconazole doses >200 mg daily **are not recommended**. If high-dose fluconazole is indicated, consider alternative ARV.
	All PIs except TPV/r	↔ PI expected ↔ fluconazole expected	No dose adjustment needed.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, monitor isavuconazole concentrations and adverse events. Monitor for virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, monitor isavuconazole concentrations and monitor for isavuconazole-related adverse events. Monitor for PI tolerability and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Itraconazole doses >200 mg/day **are not recommended** with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole concentrations.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 8 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations and monitor for posaconazole-related or PI-related adverse events.
	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	
	All other PIs	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ PI possible ↑ voriconazole possible	If coadministered, monitor voriconazole concentrations and monitor for voriconazole-related or PI-related adverse events.
	PI/c	No data	**Do not coadminister** voriconazole and RTV or COBI unless benefits outweigh risks. If coadministered, monitor voriconazole concentration and adjust dose accordingly.
	PI/r	RTV 100 mg twice daily ↓ voriconazole AUC 39%	
Antimalarials			
Artemether/ Lumefantrine	ATV (unboosted), PI/c	↑ lumefantrine expected No data for artemether	Clinical significance unknown. If coadministered, monitor closely for antimalarial efficacy and lumefantrine toxicity, including QTc prolongation.
	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 175% ↔ DRV	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 45% Lumefantrine AUC ↑ 4.8-fold ↔ LPV	
	TPV/r	↑ lumefantrine expected	**Do not coadminister**, due to risk for QTc prolongation.
Atovaquone/Proguanil	ATV/r, LPV/r	**With ATV/r:** • Atovaquone AUC ↓ 46% • Proguanil AUC ↓ 41% **With LPV/r:** • Atovaquone AUC ↓ 74% • Proguanil AUC ↓ 38%	Clinical significance unknown. Consider alternative ARV or malaria prophylaxis.
Mefloquine	All PIs	**With RTV 200 mg Twice Daily:** • RTV AUC ↓ 31% and C_{min} ↓ 43% • ↔ mefloquine **With ATV (unboosted), PI/c, or PI/r:** • No data • ↑ mefloquine possible	Clinical significance unknown. Consider alternative ARV or antimalarial drug. If coadministered, monitor for mefloquine-related adverse events, including psychiatric symptoms and QTc prolongation. Monitor virologic response.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 9 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiplatelets			
Clopidogrel	All PIs	Clopidogrel active metabolite AUC ↓ 320% with impaired platelet inhibition	**Do not coadminister.**
Prasugrel	All PIs	Prasugrel active metabolite AUC ↓ 210% with adequate platelet inhibition	Insufficient data to make a recommendation.
Ticagrelor	All PIs	↑ ticagrelor expected	**Do not coadminister**.
Vorapaxar	All PIs	↑ vorapaxar expected	**Do not coadminister**.
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	↔ atovaquone	No dose adjustment needed.
Oral suspension	All other PIs	↔ atovaquone expected	No dose adjustment needed.
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	ATV (unboosted), ATV/c, ATV/r	↑ arformoterol possible	No dose adjustment needed.
	DRV/c, DRV/r, LPV/r, TPV/r	↔ arformoterol expected	No dose adjustment needed.
Indacaterol	All PIs	**With RTV 300 mg Twice Daily:** • Indacaterol AUC ↑ 1.7-fold	No dose adjustment needed in patients receiving indacaterol 75 mcg daily.
Olodaterol	All PIs	↑ olodaterol expected	No dose adjustment needed.
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated CV events.
Cardiac Medications			
Amiodarone	TPV/r	↑ amiodarone possible ↑ PI possible	**Contraindicated.**
	All other PIs	↑ amiodarone possible ↑ PI possible	**Do not coadminister** unless benefits outweigh risks. If coadministered, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone drug concentration.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative ARV or antiarrhythmics. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister**.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister**.
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecainide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister**.
	TPV/r	↑ flecainide expected	**Contraindicated.**
Propafenone	All PIs except TPV/r	↑ propafenone possible	**Do not coadminister**.
	TPV/r	↑ propafenone expected	**Contraindicated.**
Quinidine	All PIs except TPV/r	↑ quinidine possible	**Do not coadminister**.
	TPV/r	↑ quinidine expected	**Contraindicated.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 10 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Beta-Blockers (e.g., carvedilol, metoprolol, timolol)	All PIs	↑ beta-blockers possible	May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).
Bosentan	All PIs	**With LPV/r:** • ↑ bosentan 48-fold (Day 4) and ↑ 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and unboosted ATV.** **In Patients on a PI (Other than Unboosted ATV) >10 Days:** • Start bosentan at 62.5 mg once daily or every other day. **In Patients on Bosentan who Require a PI (Other than Unboosted ATV):** • Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day. **When Switching Between COBI and RTV:** • Maintain same bosentan dose.
Calcium Channel Blockers, Except Diltiazem	All PIs	↑ dihydropyridine possible ↑ verapamil possible	Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.
Digoxin	PI/c, PI/r	RTV 200 mg twice daily ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41% and ↔ AUC	Monitor digoxin concentrations. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Diltiazem	ATV (unboosted), ATV/c, ATV/r	Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/c, DRV/r, LPV/r, TPV/r	↑ diltiazem possible	Titrate diltiazem dose according to clinical response and toxicities.
Eplerenone	PI/c, PI/r	↑ eplerenone expected	**Contraindicated.**
Ranolazine	ATV (unboosted)	↑ ranolazine possible	**Do not coadminister**.
	PI/c, PI/r	↑ ranolazine expected	**Contraindicated.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated.**
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg twice daily ↑ 17-BMP AUC 2-fold	No dose adjustment needed.
	All PIs except DRV/r	↔ 17-BMP expected	No dose adjustment needed.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 11 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg twice daily ↑ fluticasone AUC 350-fold	**Do not coadminister** unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse events associated with corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider alternative inhaled/intranasal corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	**Do not coadminister** unless potential benefits of systemic corticosteroid outweigh the risks of adverse events associated with systemic corticosteroids. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse events associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	**Do not coadminister**. Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Glucose-Lowering Medications			
Canagliflozin	ATV (unboosted), PI/c	↔ canagliflozin	No dose adjustment needed.
	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, increase canagliflozin dose to 200 mg daily. If a patient is already tolerating canagliflozin 200 mg daily and requires additional glycemic control, management strategy is based on renal function. **In Patients with eGFR ≥60 mL/min/1.73 m²:** • Canagliflozin dose may be increased to 300 mg daily. **In Patients with eGFR <60 mL/min/1.73 m²:** • Consider adding another antihyperglycemic agent.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 12 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment needed.
	TPV/r	No data	No data available for dose recommendation.
Dasabuvir plus Paritaprevir/Ombitasvir/ RTV	ATV (unboosted)	↔ ATV	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/RTV.
	ATV/c, ATV/r	No data	This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg daily without COBI or RTV. ATV should be administered in the morning, at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister**.
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister**.
	DRV/c, TPV/r	No data	**Do not coadminister**.
Elbasvir/Grazoprevir	ATV/r	Elbasvir AUC ↑ 4.8-fold Grazoprevir AUC ↑ 10.6-fold Elbasvir ↔ ATV Grazoprevir ↑ ATV AUC 43%	**Contraindicated.** May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
	DRV/r	Elbasvir AUC ↑ 66% Grazoprevir AUC ↑ 7.5-fold ↔ DRV	
	LPV/r	Elbasvir AUC ↑ 3.7-fold Grazoprevir AUC ↑ 12.9-fold ↔ LPV	
	ATV (unboosted), ATV/c, DRV/c, TPV/r	↑ grazoprevir expected	

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 13 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Glecaprevir/Pibrentasvir	ATV (unboosted), ATV/c, ATV/r	**With (ATV 300 mg plus RTV 100 mg) Once Daily:** • Glecaprevir AUC ↑ 6.5-fold • Pibrentasvir AUC ↑ 64%	**Contraindicated.**
	DRV/c, DRV/r	**With (DRV 800 mg plus RTV 100 mg) Once Daily:** • Glecaprevir AUC ↑ 5-fold • ↔ pibrentasvir	**Do not coadminister**.
	LPV/r	Glecaprevir AUC ↑ 4-fold Pibrentasvir ↑ 2.5-fold	**Do not coadminister**.
	TPV/r	↑ glecaprevir and pibrentasvir expected	**Do not coadminister**.
Ledipasvir/Sofosbuvir	ATV/r	ATV AUC ↑ 33% Ledipasvir AUC ↑ 113% ↔ sofosbuvir	No dose adjustment needed. Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased risk of TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.
	ATV (unboosted), ATV/c, DRV/c, DRV/r, LPV/r	↔ PI expected ↔ ledipasvir and sofosbuvir	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister**.
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister**.
Sofosbuvir/Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment needed.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment needed.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment needed.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected	**Do not coadminister**.
Sofosbuvir/Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	**With ATV/r:** • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister**.
	LPV/r	↑ voxilaprevir expected	**Do not coadminister**.
	DRV/c, DRV/r	**With DRV/r:** • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 14 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Sofosbuvir/Velpatasvir/ Voxilaprevir, continued	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected Effect on voxilaprevir is unknown.	**Do not coadminister**.
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Contraindicated.**
Hormonal Therapies			
Contraceptives – Injectable Depot MPA	LPV/r	MPA AUC ↑ 46% and ↔ C_{min}	No dose adjustment needed.
	All other PIs	No data	No dose adjustment needed.
Contraceptives – Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[b] or use alternative ARV or contraceptive methods. Oral contraceptives that contain less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.** Use alternative ARV or contraceptive methods.
		↔ ethinyl estradiol AUC and C_{min} ↓ 25% ↔ levonorgestrel	No dose adjustment needed.
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate AUC ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[c] Oral contraceptives that contain progestins other than norethindrone or norgestimate have not been studied.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Use alternative ARV or contraceptive methods.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% **With TPV/r:** • ↔ norethindrone AUC	**When Used for Contraception:** • Use alternative ARV or contraceptive methods. **When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation):** • Monitor for clinical effectiveness of hormonal therapy.
Contraceptives – Subdermal Implant Etonogestrel	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	No dose adjustment needed.
	All other PIs	No data	
Contraceptives – Transdermal Ethinyl Estradiol/ Norelgestromin	LPV/r	↔ LPV Ethinyl estradiol AUC ↓ 45% Norelgestromin AUC ↑ 83%	No dose adjustment needed.
	All other PIs	No data	
Contraceptives – Vaginal Ring Etonogestrel/Ethinyl Estradiol	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	No dose adjustment needed.
	All other PIs	No data	

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 15 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Contraceptives – Vaginal Ring Segesterone/Ethinyl Estradiol	All PIs	No data	Use alternative ARV or contraceptive methods.
Gender-Affirming Therapy	PI/c	↓ or ↑ estradiol possible	Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations.
	PI/r	↓ estradiol possible	
	All PIs	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	All PIs	↑ dutasteride possible ↑ finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations. No dose adjustment needed for finasteride.
	All PIs	↓ testosterone possible	Adjust testosterone dose as needed based on clinical effects and endogenous hormone concentrations.
Menopausal Replacement Therapy	All PIs	↓ or ↑ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dose as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions	Adjust progestin/progesterone dose as needed based on clinical effects. Because drospirenone is prescribed at a lower dose for menopausal HRT than the products used for hormonal contraceptives, it is not contraindicated with ATV/c products.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	ATV (unboosted), ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold and C_{max} ↑ 18.9-fold	**Do not coadminister**.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold and C_{max} ↑ 4.2-fold	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold and C_{max} ↑ 4.7-fold	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	TPV/r	Atorvastatin AUC ↑ 9.4-fold and C_{max} ↑ 8.6-fold	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 16 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying Agents, continued			
Lomitapide	All PIs except TPV/r	↑ lomitapide expected	**Contraindicated.**
	TPV/r	↑ lomitapide expected	Titrate lomitapide dose based on clinical response. Do not exceed lomitapide 30 mg daily.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ↔ ATV DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r LPV/r ↓ pitavastatin AUC 20% ↔ LPV	No dose adjustment needed.
Pravastatin	ATV/c, ATV/r	No data	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	DRV/c, DRV/r	**With DRV/r:** • Pravastatin AUC ↑ 81% following single dose of pravastatin Pravastatin AUC ↑ 23% at steady state	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment needed.
Rosuvatatin	ATV/r	Rosuvastatin AUC ↑ 3-fold and C_{max} ↑ 7-fold	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 10 mg daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold and C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold and C_{max} ↑ 3.8-fold	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48% and C_{max} ↑ 2.4-fold	Titrate rosuvastatin dose carefully and administer the lowest effective dose while monitoring for rosuvastatin-related adverse events.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold and C_{max} ↑ 4.7-fold	Titrate rosuvastatin dose carefully and administer the lowest effective dose. Do not exceed rosuvastatin 10 mg daily.
	TPV/r	Rosuvastatin AUC ↑ 26% and C_{max} ↑ 2.2-fold	No dose adjustment needed.
Simvastatin	All PIs	Significant ↑ simvastatin expected	**Contraindicated.**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine (active metabolite) AUC ↑ 76% ↓ ATV possible	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 17 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence, continued			
Buprenorphine Sublingual, buccal, or implant, continued	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 105%	Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment needed. Monitor for buprenorphine-related adverse events. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	LPV/r	↔ LPV/r	
	TPV/r	↔ buprenorphine Norbuprenorphine (active metabolite) AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV concentration. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	PI/c	No data	Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Monitor for buprenorphine-related adverse events.
Fentanyl	All PIs	↑ fentanyl possible	Monitor for fentanyl-related adverse events, including potentially fatal respiratory depression.
Lofexidine	ATV (unboosted)	↔ lofexidine expected	No dose adjustment needed.
	PI/c, PI/r	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	ATV (unboosted)	↔ ATV	No dose adjustment needed.
	PI/c	No data	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Monitor for methadone-related adverse events.
	All PI/r	ATV/r and DRV/r ↓ R-methadone[d] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% TPV/r ↓ R-methadone[d] AUC 48%	Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Oxycodone	All PIs	LPV/r ↑ oxycodone AUC 2.6-fold Other PIs: ↑ oxycodone expected	Monitor for opioid-related adverse events. Oxycodone dose reduction may be necessary.
Tramadol	All PIs	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.
PDE5 Inhibitors			
Avanafil	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
	PI/c, PI/r	RTV 600 mg twice daily (for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Do not coadminister**.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 18 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Sildenafil	All PIs	DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg twice daily ↑ sildenafil AUC 1,000%	**For Treatment of Erectile Dysfunction:** • Start with sildenafil 25 mg every 48 hours and monitor for adverse events of sildenafil. **Contraindicated** for treatment of PAH.
Tadalafil	All PIs	RTV 200 mg twice daily ↑ tadalafil AUC 124% TPV/r (first dose) ↑ tadalafil AUC 133%	**For Treatment of Erectile Dysfunction:** • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse events of tadalafil. **For Treatment of PAH** *In Patients on a PI >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require a PI:* • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients Switching between COBI and RTV:* • Maintain tadalafil dose. **For Treatment of Benign Prostatic Hyperplasia:** • Maximum recommended daily dose is tadalafil 2.5 mg per day.
Vardenafil	All PIs	RTV 600 mg twice daily ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse events of vardenafil.
Sedative/Hypnotics			
Alprazolam, Clonazepam, Diazepam	All PIs	↑ benzodiazepine possible RTV 200 mg twice daily (for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248%	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
Lorazepam, Oxazepam, Temazepam	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	**Oral midazolam is contraindicated with PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Suvorexant	All PIs	↑ suvorexant expected	**Do not coadminister**.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg twice daily ↑ triazolam half-life 1,200% and ↑ AUC 2,000%	**Contraindicated.**
Zolpidem	PI/c, PI/r	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 19 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Calcifediol	All PIs	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored.
Cisapride	All PIs	↑ cisapride expected	**Contraindicated.**
Colchicine	All PIs	RTV 100 mg twice daily ↑ colchicine AUC 296% and C_{max} ↑ 184% Significant ↑ colchicine expected with all PIs, with or without COBI or RTV	**For Treatment of Gout Flares:** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares:** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. **For Treatment of Familial Mediterranean Fever:** • Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg twice daily. **Do not coadminister in patients with hepatic or renal impairment.**
Dronabinol	All PIs	↑ dronabinol possible	Monitor for dronabinol-related adverse events.
Eluxadoline	All PIs	↑ eluxadoline expected	Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse events.
Ergot Derivatives	All PIs	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated.**
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated.**

[a] DHA is an active metabolite of artemether.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo. Generic formulations may also be available.

[c] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate: Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl. Generic formulations may also be available.

[d] R-methadone is the active form of methadone.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: 17-BMP = beclomethasone 17-monopropionate; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; FPV = fosamprenavir; H2RA = H2 receptor antagonist; HCV = hepatitis C virus; HRT = hormone replacement therapy; IDV = indinavir; INR = international normalized ratio; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MPA = medroxyprogesterone acetate; NFV = nelfinavir; OATP = organic anion-transporting polypeptide; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; PTH = parathyroid hormone; QTc = QT corrected for heart rate; RTV = ritonavir; SQV = saquinavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 12)

This table provides information on the known or predicted interactions between NNRTIs and non-ARV drugs. For information regarding interactions between NNRTIs and other ARV drugs, including dosing recommendations, refer to Tables 21c, 22a, and 22b. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Note: DLV is **not** included in this table. Please refer to the FDA product label for information regarding drug interactions between DLV and other concomitant drugs. The term "All NNRTIs" in this table refers to all NNRTIs **except for** DLV.

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	DOR, EFV, NVP	↔ NNRTI AUC	No dose adjustment needed.
	ETR	↔ ETR expected	No dose adjustment needed.
	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	DOR, ETR, NVP	↔ NNRTI expected	No dose adjustment needed.
	EFV	↔ EFV AUC	No dose adjustment needed.
	RPV	RPV AUC ↓ 76% when famotidine 40 mg is taken 2 hours prior	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	DOR	DOR AUC ↓ 17% and C_{min} ↓ 16%	No dose adjustment needed.
	EFV, NVP	↔ EFV and NVP expected	
	ETR	↔ ETR AUC	
	RPV	**With Omeprazole 20 mg Daily:** • RPV AUC ↓ 40% and C_{min} ↓ 33%	**Contraindicated.**
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin, Doxazosin, Silodosin	DOR, RPV	↔ alpha-adrenergic antagonists expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ alpha-adrenergic antagonists expected	Consider alternative ARV or alpha antagonist therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.
Tamsulosin	DOR, RPV	↔ tamsulosin expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ tamsulosin expected	Monitor for therapeutic effectiveness of tamsulosin after 2–4 weeks. May need to increase dose to tamsulosin 0.8 mg once daily for patients who fail to respond to the 0.4 mg dose.
Antibacterials			
Antimycobacterials			
Bedaquiline	DOR, RPV	↔ bedaquiline expected	No dose adjustment needed.
	EFV, ETR	↓ bedaquiline possible	**Do not coadminister.**
	NVP	↔ bedaquiline AUC	No dose adjustment needed.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterials, continued			
Antimycobacterials, continued			
Rifabutin	DOR	DOR AUC ↓ 50%	Increase DOR dose to 100 mg twice daily. No dose adjustment needed for rifabutin.
	EFV	Rifabutin ↓ 38%	The recommended dosing range is rifabutin 450–600 mg per day.
	ETR	↔ rifabutin and metabolite AUC ETR AUC ↓ 37%	**Do not coadminister ETR plus PI/r with rifabutin.** Use rifabutin 300 mg once daily if ETR is administered without PI/r.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dose adjustment needed.
	RPV	**Rifabutin plus RPV 50 mg Once Daily Compared to RPV 25 mg Once Daily Alone:** • ↔ RPV AUC and C_{min}	Increase RPV dose to 50 mg once daily. No dose adjustment for rifabutin needed.
Rifampin	DOR	DOR AUC ↓ 88%	**Contraindicated.**
	EFV	EFV AUC ↓ 26%	**Do not use EFV 400 mg with rifampin.** Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20% to 58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated.**
Rifapentine	DOR, RPV	↓ NNRTI expected	**Contraindicated.**
	EFV	↔ EFV concentrations	No dose adjustment needed.
	ETR, NVP	↓ NNRTI possible	**Do not coadminister.**
Macrolides			
Azithromycin	All NNRTIs	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	DOR, RPV	↔ clarithromycin expected ↑ DOR and RPV possible	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.
	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent (e.g., azithromycin) for MAC prophylaxis and treatment.
	ETR	Clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31% NVP AUC ↑ 26%	Monitor for effectiveness or consider alternative macrolide (e.g., azithromycin) for MAC prophylaxis and treatment.
Erythromycin	DOR, RPV	↑ DOR and RPV possible	Monitor for ARV tolerability if used in combination.
	EFV, ETR, NVP	↑ EFV, ETR, and NVP possible ↓ erythromycin possible	Monitor for antibiotic efficacy if used in combination.
Anticoagulants			
Apixaban	DOR, RPV	↔ apixaban expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ apixaban possible	Consider alternative ARV or anticoagulant therapy.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants, continued			
Betrixaban	All NNRTIs	↔ betrixaban expected	No dose adjustment needed.
Dabigatran	All NNRTIs	↔ dabigatran expected	No dose adjustment needed.
Edoxaban	All NNRTIs	↔ edoxaban expected	No dose adjustment needed.
Rivaroxaban	DOR, RPV	↔ rivaroxaban expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ rivaroxaban possible	Consider alternative ARV or anticoagulant therapy.
Warfarin	DOR, RPV	↔ warfarin expected	No dose adjustment needed.
	EFV, ETR, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	DOR, RPV	↓ NNRTI possible	**Contraindicated.**
	EFV	**Carbamazepine plus EFV:** • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% **Phenytoin plus EFV:** • ↓ EFV • ↑ or ↓ phenytoin possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor anticonvulsant and EFV concentrations.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.**
	NVP	↓ anticonvulsant and NVP possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor anticonvulsant and NVP concentrations and virologic response.
Eslicarbazepine	All NNRTIs	↓ NNRTI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Oxcarbazepine	DOR, RPV	↓ NNRTI possible	**Contraindicated.**
	EFV, ETR, NVP	↓ NNRTI possible	Consider alternative ARV or anticonvulsant. If coadministration is necessary, monitor virologic response and consider monitoring plasma concentrations of ARVs.
Ethosuximide, Lacosamide, Tiagabine, Zonisamide	DOR, RPV	↔ anticonvulsant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ anticonvulsant possible	Monitor seizure control and consider anticonvulsant therapeutic drug monitoring.
Lamotrigine	DOR, ETR, NVP, RPV	↔ lamotrigine expected	No dose adjustment needed.
	EFV	↓ lamotrigine possible	Monitor seizure control and plasma concentrations of lamotrigine.
Antidepressants, Anxiolytics, and Antipsychotics			
Antidepressants			
Bupropion	DOR, ETR, RPV	↔ bupropion expected	No dose adjustment needed.
	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
	NVP	↓ bupropion possible	

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics, continued			
Antidepressants, continued			
Citalopram, Escitalopram	DOR, RPV	↔ antidepressant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antidepressant possible	Titrate antidepressant dose based on clinical response.
Fluoxetine, Fluvoxamine	All NNRTIs	↔ antidepressant expected	No dose adjustment needed.
Paroxetine	DOR,NVP, RPV	↔ paroxetine expected	No dose adjustment needed.
	EFV, ETR	↔ paroxetine expected	No dose adjustment needed.
Nefazodone	DOR, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ nefazodone expected ↑ NNRTI possible	Monitor antidepressant effect and titrate dose as necessary based on clinical response.
Sertraline	DOR, RPV	↔ sertraline expected	No dose adjustment needed.
	EFV	Sertraline AUC ↓ 39%	Monitor the antidepressant effect and titrate dose as necessary based on clinical response.
	ETR, NVP	↓ sertraline possible	
Trazodone	DOR, RPV	↔ trazodone expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ trazodone possible	Monitor for therapeutic effectiveness of trazodone and titrate dose as necessary.
Anxiolytics (Benzodiazepines)			
Alprazolam, Triazolam	DOR, RPV	↔ benzodiazepine expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ benzodiazepine possible	Monitor for therapeutic effectiveness of benzodiazepine.
Diazepam	DOR, RPV	↔ diazepam expected	No dose adjustment needed.
	EFV, NVP	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam.
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.
Lorazepam	DOR, ETR, NVP, RPV	↔ lorazepam expected	No dose adjustment needed.
	EFV	↔ lorazepam AUC	No dose adjustment needed.
Midazolam	DOR, RPV	↔ midazolam expected	No dose adjustment needed.
	EFV	↑ or ↓ midazolam possible	Monitor for therapeutic effectiveness and toxicity of midazolam.
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite C_{max} ↑ 57%	Monitor for therapeutic effectiveness of midazolam.
	NVP	↓ midazolam possible	Monitor for therapeutic effectiveness of midazolam.
Antipsychotics			
Aripiprazole	DOR, RPV	↔ aripiprazole expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ aripiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dose recommendations.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antipsychotics, continued			
Brexpiprazole	DOR, RPV	↔ brexpiprazole expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ brexpiprazole expected	Monitor for therapeutic effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.
Cariprazine	DOR, RPV	↔ cariprazine expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ cariprazine and ↑ or ↓ active metabolite possible	**Do not coadminister.**
Lurasidone	DOR, RPV	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Olanzapine	DOR, ETR, NVP, RPV	↔ olanzapine expected	No dose adjustment needed.
	EFV	↓ olanzapine possible	Monitor for therapeutic effectiveness of olanzapine.
Pimavanserin	DOR, RPV	↔ pimavanserin expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ pimavanserin expected	**Do not coadminister.**
Pimozide	DOR, RPV	↔ pimozide expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ pimozide possible	Monitor for therapeutic effectiveness of pimozide.
Quetiapine	DOR, RPV	↔ antipsychotic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antipsychotic possible	Monitor for therapeutic effectiveness of antipsychotic.
Antifungals			
Fluconazole	DOR, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV	↔ fluconazole expected ↔ EFV AUC expected	No dose adjustment needed.
	ETR	ETR AUC ↑ 86%	No dose adjustment needed.
	NVP	NVP AUC ↑ 110%	Consider alternative ARV or antifungal agent. Increased risk of hepatotoxicity possible with this combination.
Isavuconazole	DOR, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ isavuconazole possible	Monitor isavuconazole concentration and antifungal response. Dose adjustments for isavuconazole may be necessary.
Itraconazole	DOR, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35% to 44%	**Do not coadminister, unless potential benefits outweigh the risks.** Failure to achieve therapeutic itraconazole concentrations has been reported. If coadministration is necessary, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole concentration and antifungal response.
	NVP	Itraconazole AUC ↓ 61% ↑ NVP possible	**Do not coadminister, unless potential benefits outweigh the risks.** If coadministration is necessary, monitor itraconazole concentration and adjust dose accordingly.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 6 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	DOR, ETR, NVP, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV	Posaconazole AUC ↓ 50% ↔ EFV AUC	**Do not coadminister, unless potential benefits outweigh the risks.** If coadministration is necessary, monitor posaconazole concentration and adjust dose accordingly.
Voriconazole	DOR, RPV	↑ NNRTI possible	No dose adjustment needed.
	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Adjust dose to voriconazole 400 mg twice daily plus EFV 300 mg daily.
	ETR	↔ voriconazole AUC ETR AUC ↑ 36%	No dose adjustment needed.
	NVP	↓ voriconazole possible ↑ NVP possible	Consider alternative ARV or antifungal agent. If coadministration is necessary, monitor antiretroviral tolerability and antifungal response and/or voriconazole concentration.
Antimalarials			
Artemether/ Lumefantrine	DOR, RPV	↔ antimalarial expected	No dose adjustment needed.
	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy.
	ETR	Artemether AUC ↓ 38% ↔ DHA AUC ↔ lumefantrine AUC ↔ ETR AUC	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67% to 72% **DHA:** • Study results are conflicting. DHA AUC ↓ 37% in one study, no difference in another. **Lumefantrine:** • Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in two studies but ↑ 56% in another.	Clinical significance unknown. If used in combination, monitor closely for antimalarial efficacy and lumefantrine toxicity.
Atovaquone/ Proguanil	DOR, ETR, NVP, RPV	No data	Monitor for antimalarial efficacy.
	EFV	Atovaquone AUC ↓ 75% Proguanil AUC ↓ 43%	No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 7 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiplatelets			
Clopidogrel	DOR, NVP, RPV	↔ clopidogrel expected	No dose adjustment needed.
	EFV, ETR	↓ activation of clopidogrel possible	Consider alternative ARV or antiplatelet. ETR may prevent metabolism of clopidogrel to its active metabolite.
Prasugrel	All NNRTIs	↔ prasugrel expected	No dose adjustment needed.
Ticagrelor	DOR, RPV	↔ ticagrelor expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ ticagrelor expected	Consider alternative ARV or anticoagulant therapy.
Vorapaxar	DOR, NVP, RPV	↔ vorapaxar expected	No dose adjustment needed.
	EFV, ETR	↓ vorapaxar expected	Insufficient data to make a dose recommendation.
Antipneumocystis and Anti-Toxoplasmosis Drugs			
Atovaquone (oral solution)	DOR, ETR, RPV, NVP	No data	Monitor for therapeutic effectiveness of atovaquone.
	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative ARV or agent for PCP or toxoplasmosis treatment or prophylaxis. If coadministration is necessary, monitor for therapeutic effectiveness of atovaquone.
Cardiac Medications			
Dihydropyridine CCBs	DOR, RPV	↔ CCBs expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem, Verapamil	DOR, RPV	↔ CCBs expected ↑ NNRTI possible	No dose adjustment needed.
	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	ETR, NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	DOR, EFV, ETR, NVP	↓ NNRTI possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Glucose-Lowering Agents			
Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin	All NNRTIs	↔ antihyperglycemic expected	No dose adjustment needed.
Linagliptin, Saxagliptin	DOR, RPV	↔ antihyperglycemic expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ antihyperglycemic possible	Monitor glycemic control.
Metformin	DOR	↔ metformin AUC DOR AUC ↓ 26% and C_{max} ↓ 24%	No dose adjustment needed.
	EFV, ETR, NVP, RPV	↔ metformin expected	No dose adjustment needed.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 8 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	DOR, RPV	No data	No dose adjustment needed.
	EFV, ETR, NVP	**Daclatasvir 120 mg Once Daily plus EFV 600 mg Daily Compared with Daclatasvir 60 mg Alone:** • Daclatasvir C_{min} ↓ 17% and AUC ↑ 37%	The recommended dose is daclatasvir 90 mg once daily.
Dasabuvir plus Paritaprevir/ Ombitasvir/RTV	DOR	↑ DOR possible	No dose adjustment needed.
	EFV	No data	**Contraindicated.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150% to 225%	**Do not coadminister,** due to potential for QT interval prolongation with higher concentrations of RPV.
Elbasvir/ Grazoprevir	DOR	↔ elbasvir and grazoprevir DOR AUC ↑ 56% and C_{min} ↑ 41%	No dose adjustment needed.
	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓ 83% ↔ EFV	**Contraindicated.**
	ETR, NVP	↓ elbasvir and grazoprevir expected	**Do not coadminister.**
	RPV	↔ elbasvir and grazoprevir ↔ RPV AUC and C_{min}	No dose adjustment needed.
Glecaprevir/ Pibrentasvir	DOR	↑ DOR expected	No dose adjustment needed.
	EFV	↓ glecaprevir and pibrentasvir expected	**Do not coadminister.**
	ETR	↓ glecaprevir and pibrentasvir possible	
	NVP	↓ glecaprevir and pibrentasvir possible	Consider alternative ARV or HCV regimen. If coadministration is necessary, monitor for HCV treatment efficacy.
	RPV	↔ glecaprevir and pibrentasvir RPV AUC ↑ 84%	No dose adjustment needed.
Ledipasvir/ Sofosbuvir	DOR, RPV	↔ ledipasvir and sofosbuvir ↔ DOR ↔ RPV	No dose adjustment needed.
	EFV	Ledipasvir AUC, C_{min}, and C_{max} ↓ 34% ↔ sofosbuvir	
	ETR, NVP	No significant effect expected	
Sofosbuvir/ Velpatasvir	DOR, RPV	No significant effect expected	No dose adjustment needed.
	EFV	Velpatasvir AUC ↓ 43% , C_{max} ↓ 37%, and C_{min} ↓ 47%	**Do not coadminister.**
	ETR, NVP	↓ velpatasvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir/ Voxilaprevir	DOR, RPV	No significant effect expected	No dose adjustment needed.
	EFV	Velpatasvir AUC ↓ 43% , C_{max} ↓ 37%, and C_{min} ↓47% ↓ voxilaprevir expected	**Do not coadminister.**
	ETR, NVP	↓ voxilaprevir expected ↓ velpatasvir expected	**Do not coadminister.**

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 9 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	DOR, RPV	↓ NNRTI expected	**Contraindicated.**
	EFV, ETR, NVP	↓ EFV, ETR, and NVP expected	**Do not coadminister.**
Hormonal Therapies			
Contraceptives –Injectable Depot MPA	DOR, ETR, RPV	↔ MPA expected	No dose adjustment needed.
	EFV, NVP	↔ MPA	No dose adjustment needed.
Contraceptives – Oral	DOR	↔ ethinyl estradiol ↔ levonorgestrel	No dose adjustment needed.
	EFV	↔ ethinyl estradiol Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 61% Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83% Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64%	**When Used for Contraception:** • Use alternative ARV or contraceptive methods. **When Used for Other Clinical Indications (e.g., Acne, Menstrual Cycle Regulation):** • Monitor for clinical effectiveness of hormonal therapy.
	ETR	Ethinyl estradiol AUC ↑ 22% ↔ norethindrone	No dose adjustment needed.
	NVP	Ethinyl estradiol AUC ↓ 29% and C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) C_{min} ↓ 22%	No dose adjustment needed based on clinical data that demonstrated no change in effectiveness
	RPV	↔ ethinyl estradiol ↔ norethindrone	No dose adjustment needed.
Contraceptives – Subdermal Implant Etonogestrel	DOR, RPV	↔ etonogestrel expected	No dose adjustment needed.
	EFV	Etonogestrel AUC ↓ 63% to 82%	Use alternative ARV or contraceptive methods.
	ETR	↓ etonogestrel possible	No data available to make dose recommendation.
	NVP	↔ etonogestrel	No dose adjustment needed.
Contraceptives –Subdermal Implant Levonorestrel	DOR, RPV	↔ levonorgestrel expected	No dose adjustment needed.
	EFV	Levonorgestrel AUC ↓ 47%	Use alternative ARV or contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
	ETR	↓ levonorgestrel possible	No data available to make dose recommendation.
	NVP	Levonorgestrel AUC ↑ 35%	No dose adjustment needed.
Contraceptives – Vaginal Ring Etonogestrel/ Ethinyl Estradiol	DOR, RPV	↔ etonogestrel and ethinyl estradiol expected	No dose adjustment needed.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 10 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Contraceptives – Vaginal Ring Etonogestrel/ Ethinyl Estradiol	EFV	Ethinyl estradiol (intravaginal ring) AUC ↓ 56% Etonogestrel (intravaginal ring) AUC ↓ 81%	Consider alternative ARV or contraceptive method.
	ETR, NVP	↓ etonogestrel and ethinyl estradiol possible	No data available to make dose recommendation.
Contraceptives – Vaginal Ring Segesterone/ Ethinyl Estradiol	DOR, RPV	↔ segesterone and ethinyl estradiol expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ segesterone and ethinyl estradiol possible	Consider alternative ARV or contraceptive method.
Emergency Contraceptives Levonorgestrel (oral)	DOR, RPV	↔ levonorgestrel expected	No dose adjustment needed.
	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
	NVP, ETR	↓ levonorgestrel possible	No data available to make dose recommendation.
Gender-Affirming Therapy	DOR, RPV	↔ hormonal concentrations expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ estradiol possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible	Monitor feminizing effects of estrogen and antiandrogen therapy and titrate dose as necessary to achieve therapeutic goals.
	EFV, ETR, NVP	↓ testosterone possible	Monitor masculinizing effects of testosterone and titrate testosterone dose as necessary to achieve therapeutic goals.
Menopausal Replacement Therapy	DOR, RPV	↔ hormonal concentrations expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Contraceptives – Oral for other progestin-NNRTI interactions	Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.
Immunosuppressants			
Cyclosporine	DOR, RPV	↔ cyclosporine expected ↑ NNRTI possible	No dose adjustment needed.
	EFV, ETR, NVP	↓ cyclosporine possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Everolimus, Sirolimus, Tacrolimus	DOR, RPV	↔ immunosuppressant expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 11 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying Agents			
Atorvastatin	DOR, RPV	↔ atorvastatin AUC	No dose adjustment needed.
	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	NVP	↓ atorvastatin possible	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Fluvastatin	DOR, NVP, RPV	↔ fluvastatin expected	No dose adjustment needed.
	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin, Simvastatin	DOR, RPV	↔ lovastatin and simvastatin expected	No dose adjustment needed.
	EFV	Simvastatin AUC ↓ 68% Simvastatin active metabolite AUC ↓ 60%	Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Pitavastatin	DOR, ETR, NVP, RPV	↔ pitavastatin expected	No dose adjustment needed.
	EFV	↔ pitavastatin AUC	No dose adjustment needed.
Pravastatin	DOR, NVP, RPV	↔ pravastatin expected	No dose adjustment needed.
	EFV	Pravastatin AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
	ETR	↓ pravastatin possible	
Rosuvastatin	DOR, EFV, ETR, NVP, RPV	↔ rosuvastatin expected	No dose adjustment needed.
Narcotics/Treatments for Opioid Dependence			
Buprenorphine Sublingual or buccal	DOR, RPV	↔ buprenorphine expected	No dose adjustment needed.
	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine (active metabolite) AUC ↓ 71%	No dose adjustment needed; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment needed.
	NVP	No significant effect	No dose adjustment needed.
Buprenorphine Implant	DOR, RPV	↔ buprenorphine expected	No dose adjustment needed.
	EFV, ETR, NVP	No data	Clinical monitoring is recommended when NNRTI is initiated after insertion of buprenorphine implant.
Lofexidine	DOR, EFV, ETR, NVP, RPV	↔ lofexidine expected	No dose adjustment needed.
Methadone	DOR, ETR	No significant effect	No dose adjustment needed.
	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; monitor and increase methadone dose as necessary.
	NVP	Methadone AUC ↓ 37% to 51% ↔ NVP	Opioid withdrawal common; monitor and increase methadone dose as necessary.
	RPV	R-methadone[a] AUC ↓ 16%	No dose adjustment needed, but monitor for withdrawal symptoms.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 12 of 12)

Concomitant Drug	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Sildenafil	DOR	↔ sildenafil expected	No dose adjustment needed.
	EFV, NVP	↓ sildenafil possible	May need to titrate sildenafil dose based on clinical effect.
	ETR	Sildenafil AUC ↓ 57%	May need to titrate sildenafil dose based on clinical effect.
	RPV	↔ sildenafil AUC and C_{max}	No dose adjustment needed.
Tadalafil	DOR, RPV	↔ tadalafil expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ tadalafil possible	May need to titrate tadalafil dose based on clinical effect.
Avanafil, Vardenafil	DOR, RPV	↔ avanafil or vardenafil expected	No dose adjustment needed.
	EFV, ETR, NVP	↓ avanafil or vardenafil possible	May need to increase PDE5 inhibitor dose based on clinical effect.

[a] R-methadone is the active form of methadone.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: ARV = antiretroviral; AUC = area under the curve; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAA = direct-acting antiviral; DHA = dihydroartemisinin; DLV = delavirdine; DOR = doravirine; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; HCV = hepatitis C virus; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; MPA = medroxyprogesterone acetate; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jirovecii* pneumonia; PDE5 = phosphodiesterase type 5; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

Table 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 3)

This table provides information on the known or predicted interactions between NRTIs and non-ARV drugs. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Note: Interactions associated with ddI and d4T are **not** included in this table. Please refer to the FDA product labels for ddI and d4T for information regarding drug interactions between these NRTIs and other drugs.

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cytomegalovirus and Hepatitis B Antivirals			
Adefovir	TAF, TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may increase.
Ganciclovir, Valganciclovir	TAF, TDF	No data	Serum concentrations of ganciclovir and/or TFV may increase. Monitor for dose-related toxicities.
	ZDV	↔ ZDV expected ↔ ganciclovir expected	If coadministered, closely monitor for hematologic toxicities.
Hepatitis C Antiviral Agents			
Glecaprevir/ Pibrentasvir	TAF	↔ TFV AUC	No dose adjustment needed.
	TDF	TFV AUC ↑ 29%	No dose adjustment needed.
Ledipasvir/ Sofosbuvir	TAF	TFV AUC ↑ 27%	No dose adjustment needed.
	TDF	Ledipasvir ↑ TFV AUC 40% to 98% when TDF is given with RPV and EFV Ledipasvir ↑ TFV C_{min} 55% to 80% when TDF is given with various PIs, NNRTIs, or INSTIs Further ↑ TFV AUC and C_{max} possible when TDF is given with PIs	**Do not coadminister** with EVG/c/TDF/FTC. If TDF is used in these patients, monitor for TDF toxicities. Consider using TAF in patients at risk of TDF-associated adverse events. Consider using TAF or alternative HCV therapy in patients on TDF plus a PI/r or PI/c. The safety of increased TFV exposure with this combination has not been established.
Ribavirin	TDF	**Ribavirin With Sofosbuvir 400 mg:** • ↔ TFV AUC	No dose adjustment needed.
	ZDV	Ribavirin inhibits phosphorylation of ZDV	Consider alternative. If coadministered, closely monitor HIV virologic response and monitor for possible hematologic toxicities.
Sofosbuvir/ Velpatasvir	TAF	↔ TAF expected	No dose adjustment needed.
	TDF	TFV C_{max} and AUC ↑ 39% to 81% when coadministered with various ARV combinations	If TDF is used in these patients, monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	TAF	↔ TAF expected	No dose adjustment needed.
	TDF	TFV C_{max} and AUC ↑ 35% to 55% when coadministered with various ARV combinations	If TDF is used in these patients, monitor for TDF-related toxicities. Consider using TAF in patients at risk of TDF-related adverse events.

Table 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 3)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
INSTIs			
DTG	TAF	↔ TAF AUC	No dose adjustment needed.
	TDF	↔ TDF AUC ↔ DTG AUC	No dose adjustment needed.
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment needed.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine	3TC, TDF, ZDV	↔ 3TC, TDF, ZDV, and buprenorphine	No dose adjustment needed.
	TAF	↔ TAF expected	No dose adjustment needed.
Methadone	ABC	Methadone clearance ↑ 22%	No dose adjustment needed.
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
Other			
Anticonvulsants Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	TAF	**With Carbamazepine:** • TAF AUC ↓ 55% ↓ TAF possible with other anticonvulsants	**Do not coadminister.**
Antimycobacterial Rifampin	TAF	**TAF with Rifampin Compared with TDF Alone:** • TFV-DP AUC ↑ 4.2-fold **TAF with Rifampin Compared with TAF Alone:** • TAF AUC ↓ 55% • TFV-DP AUC ↓ 36% **TAF 25 mg Twice Daily with Rifampin Compared with TAF Once Daily Alone:** • TAF AUC ↓ 14% • TFV-DP AUC ↓ 24%	**Do not coadminister, unless benefits outweigh risks.** Intracellular TFV-DP levels are higher when TAF is coadministered with rifampin compared to TDF administered alone, but clinical outcomes have not been studied. If coadministered, monitor virologic response.
	TDF	↔ AUC TFV	No dose adjustment needed.
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Rifabutin, Rifapentine	TAF	↓ TAF possible	**Do not coadminister.**
St. John's Wort	TAF	↓ TAF possible	**Do not coadminister.**
PIs for Treatment of HIV			
ATV (Unboosted), ATV/c, ATV/r	TAF	**TAF 10 mg with ATV/r:** • TAF AUC ↑ 91% **TAF 10 mg with ATV/c:** • TAF AUC ↑ 75%	No dose adjustment needed (use TAF 25 mg).

Table 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 3)

Concomitant Drug	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
ATV (Unboosted), ATV/c, ATV/r	TDF	**With ATV (Unboosted):** • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) TFV AUC ↑ 24% to 37%	**Do not coadminister unboosted ATV with TDF.** Use ATV 300 mg daily plus (RTV 100 mg or COBI 150 mg) daily when coadministering TDF 300 mg daily. If using TDF and an H2 receptor antagonist in an ART-experienced patient, use ATV 400 mg daily plus (RTV 100 mg or COBI 150 mg) daily. Monitor for TDF-associated toxicities.
	ZDV	**With ATV (Unboosted):** • ZDV C_{min} ↓ 30% and ↔ ZDV AUC	Clinical significance unknown. If coadministered, monitor virologic response.
DRV/c	TAF	**TAF 25 mg with DRV/c:** • ↔ TAF	No dose adjustment needed.
	TDF	↑ TFV possible	Monitor for TDF-associated toxicities.
DRV/r	TAF	**TAF 10 mg with DRV/r:** • ↔ TAF AUC	No dose adjustment needed.
	TDF	TFV AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. If coadministered, monitor for TDF-associated toxicities.
LPV/r	TAF	**TAF 10 mg with DRV/r:** • TAF AUC ↑ 47%	No dose adjustment needed.
	TDF	↔ LPV/r AUC TFV AUC ↑ 32%	Clinical significance unknown. If coadministered, monitor for TDF-associated toxicities.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Clinical significance unknown. If coadministered, monitor virologic response.
	TAF	↓ TAF expected	**Do not coadminister, unless benefits outweigh risks.**
	TDF	↔ TDF AUC TPV AUC ↓ 9% to 18% and C_{min} ↓ 12% to 21%	No dose adjustment needed.
	ZDV	ZDV AUC ↓ 31% to 42% ↔ TPV AUC	Clinical significance unknown. If coadministered, monitor virologic response.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 17)

This table provides information on the known or predicted interactions between INSTIs (BIC, DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. For information regarding interactions between INSTIs and other ARV drugs, including dosing recommendations, refer to Tables 21c, 22a, and 22b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Al, Mg, +/- Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe and Ca supplements, multivitamins).	BIC	**Al/Mg Hydroxide Antacid:** • ↔ BIC AUC if antacid is administered 2 hours after BIC and under fasting conditions • BIC AUC ↓ 52% if antacid is administered 2 hours before BIC • BIC AUC ↓ 47% to 79% if administered simultaneously with antacid **$CaCO_3$ Antacid:** • ↔ BIC AUC if administered with food • BIC AUC ↓ 33% if administered under fasting conditions	**With Antacids That Contain Al/Mg:** • Administer antacids that contain Al/Mg at least 2 hours after or 6 hours before BIC. **With Antacids That Contain Ca:** • Administer BIC and antacids that contain Ca together with food. • **Do not coadminister BIC simultaneously with antacids that contain Ca on an empty stomach.**
	DTG	DTG AUC ↓ 74% if administered simultaneously with antacid DTG AUC ↓ 26% if administered 2 hours before antacid	Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if administered simultaneously with antacid EVG AUC ↓ 15% to 20% if administered 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c and antacid administration by more than 2 hours.
	RAL	**Al/Mg Hydroxide Antacid:** • RAL C_{min} ↓ 49% to 63% **$CaCO_3$ Antacid:** • RAL 400 mg twice daily: C_{min} ↓ 32% • RAL 1,200 mg once daily: C_{min} ↓ 48% to 57%	**Do not coadminister RAL and Al/Mg hydroxide antacids.** Use alternative acid-reducing agent. **With $CaCO_3$ Antacids:** • RAL 1,200 mg once daily: **Do not coadminister.** • RAL 400 mg twice daily: No dose adjustment or separation needed.
H2-Receptor Antagonists	BIC, DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Proton Pump Inhibitors	BIC, DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment needed.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, DTG, RAL	↔ alfuzosin expected	No dose adjustment needed.
	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	BIC, DTG, RAL	↔ doxazosin expected	No dose adjustment needed.
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate based on doxazosin efficacy and adverse events. Doxazosin dose reduction may be needed.
Tamsulosin	BIC, DTG, RAL	↔ tamsulosin expected	No dose adjustment needed.
	EVG/c	↑ tamsulosin expected	**Do not coadminister, unless benefits outweigh risks.** If coadministered, monitor for tamsulosin-related adverse events.
Terazosin	BIC, DTG, RAL	↔ terazosin expected	No dose adjustment needed.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose and titrate based on terazosin efficacy and adverse events. Terazosin dose reduction may be necessary.
Silodosin	BIC, DTG, RAL	↔ silodosin expected	No dose adjustment needed.
	EVG/c	↑ silodosin expected	**Contraindicated.**
Antibacterials			
Antimycobacterials			
Rifabutin	BIC	**Rifabutin 300 mg Once Daily:** • BIC AUC ↓ 38% and C_{min} ↓ 56%	**Do not coadminister.**
	DTG	**Rifabutin 300 mg Once Daily:** • ↔ DTG AUC and C_{min} ↓ 30%	No dose adjustment needed.
	EVG/c	**Rifabutin 150 mg Every Other Day with EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone:** • ↔ rifabutin AUC • 25-O-desacetyl-rifabutin AUC ↑ 625% • EVG AUC ↓ 21% and C_{min} ↓ 67%	**Do not coadminister.**
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	BIC	BIC AUC ↓ 75%	**Contraindicated.**
	DTG	**Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone:** • DTG AUC ↓ 54% and C_{min} ↓ 72% **Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone:** • DTG AUC ↑ 33% and C_{min} ↑ 22%	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily) in patients without suspected or documented INSTI-associated resistance mutations. Consider an alternative to rifampin, such as rifabutin, in patients with certain suspected or documented INSTI-associated resistance mutations.
	EVG/c	Significant ↓ EVG and COBI expected	**Contraindicated.**
	RAL	**RAL 400 mg:** • RAL AUC ↓ 40% and C_{min} ↓ 61% **Rifampin with RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone:** • RAL AUC ↑ 27% and C_{min} ↓ 53%	Use RAL 800 mg twice daily instead of 400 mg twice daily. **Do not coadminister RAL 1,200 mg once daily with rifampin.** Monitor closely for virologic response, or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, DTG, EVG/c	Significant ↓ BIC, DTG, EVG, and COBI expected	**Do not coadminister.**
	RAL	**Rifapentine 900 mg Once Weekly:** • RAL AUC ↑ 71% and C_{min} ↓ 12% **Rifapentine 600 mg Once Daily:** • RAL C_{min} ↓ 41%	For once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustment needed. **Do not coadminister with once-daily rifapentine.**
Macrolides			
Azithromycin	All INSTIs	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ clarithromycin expected	No dose adjustment needed.
	EVG/c	↑ clarithromycin expected ↑ COBI possible	Reduce clarithromycin dose by 50% in patients with CrCl 50 to 60 mL/min. **Do not coadminister in patients with CrCl <50 mL/min.** Consider alternative ARV or use azithromycin.
Erythromycin	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ erythromycin expected	No dose adjustment needed.
	EVG/c	↑ erythromycin expected ↑ COBI possible	No data available for dose recommendation. Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	BIC, DTG, RAL	↔ apixaban expected	No dose adjustment needed.
	EVG/c	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. Reduce apixaban dose by 50% in patients who require apixaban 5 mg or 10 mg twice daily.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants, continued			
Betrixaban	BIC, DTG, RAL	↔ betrixaban expected	No dose adjustment needed.
	EVG/c	↑ betrixaban expected	Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily.
Dabigatran	BIC, DTG, RAL	↔ dabigatran expected	No dose adjustment needed.
	EVG/c	↑ dabigatran expected **With COBI 150 mg Alone:** • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.
Edoxaban	BIC, DTG, RAL	↔ edoxaban expected	No dose adjustment needed.
	EVG/c	↔ or ↑ edoxaban expected	**Stroke Prevention in Nonvalvular Atrial Fibrillation:** • No dose adjustment needed. **Deep Venous Thrombosis and Pulmonary Embolism:** • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, DTG, RAL	↔ rivaroxaban expected	No dose adjustment needed.
	EVG/c	↑ rivaroxaban expected	**Do not coadminister.**
Warfarin	BIC, DTG, RAL	↔ warfarin expected	No dose adjustment needed.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	**Do not coadminister.**
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg twice daily in ART-naive or ART-experienced, INSTI-naive patients. **Do not coadminister in INSTI-experienced patients with known or suspected INSTI resistance.**
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Do not coadminister.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider alternative ARV or anticonvulsant.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Ethosuximide	BIC, DTG, RAL	↔ ethosuximide expected	No dose adjustment needed.
	EVG/c	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	BIC, DTG, RAL	↔ lamotrigine expected	No dose adjustment needed.
	EVG/c	No data	Monitor anticonvulsant concentrations and adjust dose accordingly.
Oxcarbazepine	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c, RAL	↓ EVG/c and RAL possible	Consider alternative ARV or anticonvulsant.
Phenobarbital Phenytoin	BIC	↓ BIC possible	**Do not coadminister.**
	DTG	↓ DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Do not coadminister.**
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.
Antidepressants, Anxiolytics, Antipsychotics Also see Sedative/Hypnotics section below			
Aripiprazole	BIC, DTG, RAL	↔ aripiprazole expected	No dose adjustment needed.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on aripiprazole efficacy and adverse events. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, DTG, RAL	↔ brexpiprazole expected	No dose adjustment needed.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on brexpiprazole efficacy and adverse events. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Bupropion	BIC, DTG, RAL	↔ bupropion expected	No dose adjustment needed.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, DTG, RAL	↔ buspirone expected	No dose adjustment needed.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Buspirone dose reduction may be needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 6 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, Antipsychotics, continued Also see Sedative/Hypnotics section below			
Cariprazine	BIC, DTG, RAL	↔ cariprazine expected	No dose adjustment needed.
	EVG/c	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving EVG/c:** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of 3 mg daily. If EVG/c is withdrawn, cariprazine dose may need to be increased. **Starting EVG/c in a Patient Who is Already Receiving Cariprazine:** • For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day. If EVG/c is withdrawn, cariprazine dose may need to be increased.
Iloperidone	BIC, DTG, RAL	↔ iloperidone expected	No dose adjustment needed.
	EVG/c	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lurasidone	BIC, DTG, RAL	↔ lurasidone expected	No dose adjustment needed.
	EVG/c	↑ lurasidone expected	**Contraindicated.**
Nefazodone	BIC, DTG, RAL	↔ nefazodone expected	No dose adjustment needed.
	EVG/c	↑ nefazodone expected	Consider alternative ARV or antidepressant.
Pimavanserin	BIC, DTG, RAL	↔ pimavanserin expected	No dose adjustment needed.
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg.
Pimozide	BIC, DTG, RAL	↔ pimozide expected	No dose adjustment needed.
	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	BIC, DTG, RAL	↔ quetiapine expected	No dose adjustment needed.
	EVG/c	↑ quetiapine AUC expected	**Starting Quetiapine in a Patient Receiving EVG/c:** • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse events. **Starting EVG/c in a Patient Receiving a Stable Dose of Quetiapine:** • Reduce quetiapine dose to 1/6 of the current dose, and closely monitor for quetiapine efficacy and adverse events.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 7 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, Antipsychotics, continued Also see Sedative/Hypnotics section below			
Selective Serotonin Reuptake Inhibitors Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	EVG/c	↔ EVG ↔ sertraline	No dose adjustment needed.
		↑ other SSRIs possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	BIC, DTG, RAL	↔ BIC, DTG and RAL expected ↔ SSRI expected	No dose adjustment needed.
Tricyclic Antidepressants Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, DTG, RAL	↔ TCA expected	No dose adjustment needed.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug concentrations.
Trazodone	BIC, DTG, RAL	↔ trazodone expected	No dose adjustment needed.
	EVG/c	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Ziprasidone	BIC, DTG, RAL	↔ ziprasidone expected	No dose adjustment needed.
	EVG/c	↑ ziprasidone possible	Monitor for ziprasidone-related adverse events.
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., perphenazine, risperidone, thioridazine)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Antipsychotic dose reduction may be needed.
Antifungals			
Isavuconazole	BIC	↑ BIC possible	No dose adjustment needed.
	EVG/c	↑ isavuconazole expected ↑ or ↓ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ itraconazole expected	No dose adjustment needed.
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole concentrations to guide dose adjustments. **Do not coadminister with high itraconazole doses (>200 mg/day) unless guided by itraconazole concentrations.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 8 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	BIC	↑ BIC expected	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ posaconazole expected	No dose adjustment needed.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ voriconazole expected	No dose adjustment needed.
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister voriconazole and COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for adverse events of metformin.
	DTG	**DTG 50 mg Once Daily plus Metformin 500 mg Twice Daily:** • Metformin AUC ↑ 79% and C_{max} ↑ 66% **DTG 50 mg Twice Daily plus Metformin 500 mg Twice Daily:** • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for adverse events of metformin. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse events of metformin.
	RAL	↔ metformin expected	No dose adjustment needed.
Saxagliptin	BIC, DTG, RAL	↔ saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	BIC, DTG, RAL	↔ dapagliflozin or saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended**.
Antiplatelets			
Clopidogrel	BIC, DTG, RAL	↔ clopidogrel expected	No dose adjustment needed.
	EVG/c	↓ clopidogrel active metabolite, with impaired platelet inhibition expected	**Do not coadminister.**
Prasugrel	BIC, DTG, RAL	↔ prasugrel expected	No dose adjustment needed.
	EVG/c	↓ prasugrel active metabolite, with no impairment of platelet inhibition expected	Insufficient data to make a dose recommendation.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 9 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiplatelets, continued			
Ticagrelor	BIC, DTG, RAL	↔ ticagrelor expected	No dose adjustment needed.
	EVG/c	↑ ticagrelor expected	**Do not coadminister.**
Vorapaxar	BIC, DTG, RAL	↔ vorapaxar expected	No dose adjustment needed.
	EVG/c	↑ vorapaxar expected	**Do not coadminister.**
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	All INSTIs	↔ arformoterol or formoterol expected	No dose adjustment needed.
Indacaterol	BIC, DTG, RAL	↔ indacaterol expected	No dose adjustment needed.
	EVG/c	↑ indacaterol expected	
Olodaterol	BIC, DTG, RAL	↔ olodaterol expected	No dose adjustment needed.
	EVG/c	↑ olodaterol expected	
Salmeterol	BIC, DTG, RAL	↔ salmeterol expected	No dose adjustment needed.
	EVG/c	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events.
Cardiac Medications			
Amiodarone	BIC, DTG, RAL	↔ INSTI expected ↔ amiodarone expected	No dose adjustment needed.
	EVG/c	↑ INSTI possible ↑ amiodarone possible	**Do not coadminister, unless benefits outweigh risks.** If coadministration is necessary, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone concentrations.
Bepridil, Digoxin, Disopyramide, Dronedarone, Flecainide, Systemic Lidocaine, Mexilitine, Propafenone, Quinidine	BIC, DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment needed. Monitor for disopyramide-related adverse events.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment needed.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and ↔ AUC	Therapeutic drug monitoring for antiarrhythmics, if available, is recommended.
Beta-Blockers (e.g., metoprolol, timolol)	BIC, DTG, RAL	↔ beta-blocker expected	No dose adjustment needed.
	EVG/c	↑ beta-blocker possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using an alternative ARV, or a beta-blocker that is not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 10 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Bosentan	BIC, DTG	↓ BIC and DTG possible	No dose adjustment needed.
	RAL	↔ bosentan expected	No dose adjustment needed.
	EVG/c	↑ bosentan possible	**In Patients on EVG/c ≥10 Days:** • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. **In Patients on Bosentan Who Require EVG/c:** • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Calcium Channel Blockers	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ CCB expected	No dose adjustment needed.
	EVG/c	↑ CCB possible	Titrate CCB dose and monitor for CCB efficacy and adverse events.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated.**
	RAL	↔ dofetilide expected	No dose adjustment needed.
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, DTG, RAL	↔ eplerenone expected	No dose adjustment needed.
	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ivabradine	BIC, DTG, RAL	↔ ivabradine expected	No dose adjustment needed.
	EVG/c	↑ ivabradine expected	**Contraindicated.**
Ranolazine	BIC, DTG, RAL	↔ ranolazine expected	No dose adjustment needed.
	EVG/c	↑ ranolazine expected	**Contraindicated.**
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, DTG, EVG/c, RAL	↔ glucocorticoid expected	No dose adjustment needed.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid possible	**Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider using an alternative corticosteroid (e.g., beclomethasone).

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 11 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Betamethasone, Budesonide Systemic	BIC, DTG, RAL	↔ INSTI expected ↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoids possible ↓ EVG possible	**Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	BIC	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	DTG, RAL	↔ INSTI expected	No dose adjustment needed.
	EVG/c	↓ EVG and COBI possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministration is necessary, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	BIC, RAL	No data	No dose adjustment needed.
	DTG	↔ daclatasvir	No dose adjustment needed.
	EVG/c	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Dasabuvir plus Ombitasvir/Paritaprevir/RTV	BIC, DTG	No data	No dose adjustment needed.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment needed.
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment needed.
	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 12 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Elbasvir/Grazoprevir	EVG/c	↑ elbasvir expected ↑ grazoprevir expected	**Do not coadminister.**
	RAL	↔ elbasvir ↔ grazoprevir ↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment needed.
Glecaprevir/Pibrentasvir	BIC	↔ BIC expected	No dose adjustment needed.
	DTG, RAL	No significant effect	No dose adjustment needed.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
Ledipasvir/Sofosbuvir	BIC, DTG, RAL	↔ DTG and RAL	No dose adjustment needed.
	EVG/c/ TDF/FTC	↑ TDF expected ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/ TAF/FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment needed.
Sofosbuvir	All INSTIs	↔ INSTI expected ↔ sofosbuvir expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir	All INSTIs	↔ INSTI expected ↔ sofosbuvir and velpatasvir expected	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events.
Sofosbuvir/Velpatasvir/ Voxilaprevir	EVG/c	**When Administered with Sofosbuvir/ Velpatasvir/Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg:** • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
	BIC, DTG, RAL	↔ INSTI expected ↔ sofosbuvir, velpatasvir, and voxilaprevir expected	No dose adjustment needed.
Herbal Products			
St. John's Wort	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI expected	**Contraindicated.**
Hormonal Therapies			
Contraceptives: Non-Oral	All INSTIs	No data	No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear whether drug-drug interaction data for oral drugs can be used to predict interactions for non-oral drugs.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 13 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Contraceptives – Oral	BIC, DTG, RAL	↔ ethinyl estradiol and norgestimate ↔ INSTI	No dose adjustment needed.
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and may include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of using the drug and consider using an alternative ARV or contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended, due to the potential for hyperkalemia. Consider using alternative ARV or contraceptive method.
Gender-Affirming Therapy	BIC, DTG, EVG/c, RAL	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	BIC, DTG, RAL	↔ estrogen expected	No dose adjustment needed.
		↔ testosterone expected	No dose adjustment needed.
	EVG/c	↓ or ↑ estradiol possible ↑ dutasteride and finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations.
		↑ testosterone possible	Monitor masculinizing effects of testosterone and monitor for adverse effects. Adjust testosterone dose as necessary.
Menopausal Replacement Therapy	BIC, DTG, RAL	↔ estrogen expected with estradiol or conjugated estrogen (equine and synthetic) ↔ drospirenone, medroxyprogesterone, and micronized progesterone expected	No dose adjustment needed.
	EVG/c	↓ or ↑ estrogen possible ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, DTG, RAL	↔ immunosuppressant expected	No dose adjustment needed.
	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	BIC, DTG, RAL	↔ atorvastatin expected	No dose adjustment needed.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully and administer the lowest effective dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 14 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying Agents, continued			
Lomitapide	BIC, DTG, RAL	↔ lomitapide expected	No dose adjustment needed.
	EVG/c	↑ lomitapide expected	**Contraindicated.**
Lovastatin	BIC, DTG, RAL	↔ lovastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin, Pravastatin	BIC, DTG, RAL	↔ statin expected	No dose adjustment needed.
	EVG/c	No data	No data available for dose recommendation.
Rosuvastatin	BIC, DTG, RAL	↔ rosuvastatin expected	No dose adjustment needed.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest effective dose while monitoring for adverse events.
Simvastatin	BIC, DTG, RAL	↔ simvastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated.**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, DTG	↔ buprenorphine and norbuprenorphine (active metabolite) expected	No dose adjustment needed.
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment needed. Monitor for adverse events of buprenorphine. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ buprenorphine and norbuprenorphine (active metabolite) (sublingual) ↔ buprenorphine or norbuprenorphine (active metabolite) expected (implant)	No dose adjustment needed.
Fentanyl	BIC, DTG, RAL	↔ fentanyl expected	No dose adjustment needed.
	EVG/c	↑ fentanyl	Monitor for fentanyl efficacy and adverse events, including potentially fatal respiratory depression.
Lofexidine	BIC, DTG, RAL	↔ lofexidine expected	No dose adjustment needed.
	EVG/c	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	All INSTIs	↔ methadone	No dose adjustment needed.
Tramadol	BIC, DTG, RAL	↔ tramadol and M1 (active metabolite) expected	No dose adjustment needed.
	EVG/c	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.

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Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	BIC, DTG, RAL	↔ avanafil expected	No dose adjustment needed.
	EVG/c	No data	**Do not coadminister.**
Sildenafil	BIC, DTG, RAL	↔ sildenafil expected	No dose adjustment needed.
	EVG/c	↑ sildenafil expected	**For Treatment of Erectile Dysfunction:** • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. **Contraindicated** for treatment of PAH.
Tadalafil	BIC, DTG, RAL	↔ tadalafil expected	No dose adjustment needed.
	EVG/c	↑ tadalafil expected	**For Treatment of Erectile Dysfunction:** • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil. **For Treatment of PAH** *In Patients on EVG/c >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/c:* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, DTG, RAL	↔ vardenafil expected	No dose adjustment needed.
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Buspirone	BIC, DTG, RAL	↔ buspirone expected	No dose adjustment needed.
	EVG/c	↑ buspirone expected	Initiate buspirone at a low dose. Dose reduction may be needed.
Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, DTG, RAL	↔ benzodiazepine expected	No dose adjustment needed.
	EVG/c	↑ benzodiazepine possible	Dose reduction of benzodiazepine may be necessary. Initiate with a low dose and monitor for benzodiazepine-related adverse events. Consider using an alternative benzodiazepine, such as lorazepam, oxazepam, or temazepam.
Midazolam, Triazolam	BIC, RAL	↔ benzodiazepine expected	No dose adjustment needed.

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Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sedative/Hypnotics, continued			
Midazolam, Triazolam, continued	DTG	**With DTG 25 mg:** • ↔ midazolam AUC	No dose adjustment needed.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c.** Parenteral midazolam can be administered in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.
Suvorexant	BIC, DTG, RAL	↔ suvorexant expected	No dose adjustment needed.
	EVG/c	↑ suvorexant expected	**Do not coadminister.**
Zolpidem	BIC, DTG, RAL	↔ zolpidem expected	No dose adjustment needed.
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction of zolpidem may be necessary.
Miscellaneous Drugs			
Calcifediol	BIC, DTG, RAL	↔ calcifediol expected	No dose adjustment needed.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required. Monitor serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations.
Cisapride	BIC, DTG, RAL	↔ cisapride expected	No dose adjustment needed.
	EVG/c	↑ cisapride expected	**Contraindicated.**
Colchicine	BIC, DTG, RAL	↔ colchicine expected	No dose adjustment needed.
	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** **For Treatment of Gout Flares:** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares:** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. **For Treatment of Familial Mediterranean Fever:** • Do not exceed colchicine 0.6 mg once daily or 0.3 mg twice daily.
Dronabinol	BIC, DTG, RAL	↔ dronabinol expected	No dose adjustment needed.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse events.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 17 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
Eluxadoline	BIC, DTG, RAL	↔ eluxadoline expected	No dose adjustment needed.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse events.
Ergot Derivatives	BIC, DTG, RAL	↔ dihydroergotamine, ergotamine, and methylergonovine expected	No dose adjustment needed.
	EVG/c	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated.**
Flibanserin	BIC, DTG, RAL	↔ flibanserin expected	No dose adjustment needed.
	EVG/c	↑ flibanserin expected	**Contraindicated.**
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals **Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	BIC	↔ BIC AUC if administered simultaneously with Fe or Ca and food BIC AUC ↓ 33% if administered simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if administered simultaneously with Fe under fasting conditions	**With Supplements That Contain Ca or Fe:** • Administer BIC and supplements that contain Ca or Fe together with food. **Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.**
	DTG	DTG AUC ↓ 39% if administered simultaneously with $CaCO_3$ under fasting conditions DTG AUC ↓ 54% if administered simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	**With Supplements That Contain Ca or Fe:** • Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement. **Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.**
	EVG/c, RAL	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 6 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; AUC = area under the curve; BIC = bictegravir; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DAA = direct-acting antiviral; DTG = dolutegravir; ECG = electrocardiogram; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; HCV = hepatitis C virus; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PTH = parathyroid hormone; RAL = raltegravir; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; Zn = zinc

Table 21e. Drug Interactions between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 3)

In the table below, "No dose adjustment needed" indicates that the FDA-approved dose of MVC 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Concomitant Drug Class/Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antibacterial Agents		
Antimycobacterials		
Rifabutin	↓ MVC possible	**If Used Without a Strong CYP3A Inhibitor:** • MVC 300 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • MVC 150 mg twice daily
Rifampin	MVC AUC ↓ 63%	**If Used Without a Strong CYP3A Inhibitor:** • MVC 600 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • Consider alternative ARV or antimycobacterial.
Rifapentine	↓ MVC expected	**Do not coadminister.**
Macrolides		
Azithromycin	↔ MVC expected	No dose adjustment needed.
Clarithromycin	↑ MVC possible	MVC 150 mg twice daily
Erythromycin	↑ MVC possible	No dose adjustment needed.
Anticonvulsants		
Carbamazepine, Phenobarbital, Phenytoin	↓ MVC possible	**If Used Without a Strong CYP3A Inhibitor:** • MVC 600 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • MVC 150 mg twice daily
Eslicarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Oxcarbazepine	↓ MVC possible	Consider alternative ARV or anticonvulsant.
Antifungals		
Fluconazole	↑ MVC possible	No dose adjustment needed.
Isavuconazole	↑ MVC possible	No dose adjustment needed.
Itraconazole	↑ MVC possible	MVC 150 mg twice daily
Posaconazole	↑ MVC possible	MVC 150 mg twice daily
Voriconazole	↑ MVC possible	MVC 150 mg twice daily
Hepatitis C Direct-Acting Antivirals		
Daclatasvir	↔ MVC expected ↔ daclatasvir expected	No dose adjustment needed.
Dasabuvir plus Ombitasvir/ Paritaprevir/RTV	↑ MVC expected	**Do not coadminister.**
Elbasvir/Grazoprevir	↔ MVC expected	No dose adjustment needed.

Table 21e. Drug Interactions between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 3)

Concomitant Drug Class/Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antivirals, continued		
Glecaprevir/Pibrentasvir	↔ MVC expected	No dose adjustment needed.
Ledipasvir/Sofosbuvir	↔ MVC expected	No dose adjustment needed.
Simeprevir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir	↔ MVC expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir/Voxilaprevir	↔ MVC expected	No dose adjustment needed.
Herbal Products		
St. John's Wort	↓ MVC expected	**Do not coadminister.**
Hormonal Therapies		
Hormonal Contraceptives	↔ ethinyl estradiol or levonorgestrel	No dose adjustment needed.
Menopausal Hormone Replacement Therapy	↔ MVC or hormone replacement therapies expected	No dose adjustment needed.
Gender-Affirming Hormone Therapies	↔ MVC or gender-affirming hormones expected	No dose adjustment needed.
Antiretroviral Drugs		
INSTIs		
BIC, DTG	↔ MVC expected	No dose adjustment needed.
EVG/c	↑ MVC possible	MVC 150 mg twice daily
RAL	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dose adjustment needed.
NNRTIs		
DOR, RPV	↔ MVC expected	No dose adjustment needed.
EFV	MVC AUC ↓ 45%	**If Used Without a Strong CYP3A Inhibitor:** • MVC 600 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • MVC 150 mg twice daily
ETR	MVC AUC ↓ 53%	**If Used Without a Strong CYP3A Inhibitor:** • MVC 600 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • MVC 150 mg twice daily
NVP	↔ MVC AUC	**If Used Without a Strong CYP3A Inhibitor:** • MVC 300 mg twice daily **If Used With a Strong CYP3A Inhibitor:** • MVC 150 mg twice daily • With TPV/r, use MVC 300 mg twice daily
PIs		
ATV, ATV/c, ATV/r	**With Unboosted ATV:** • MVC AUC ↑ 257% **With (ATV/r 300 mg/100 mg) Once Daily:** • MVC AUC ↑ 388%	MVC 150 mg twice daily

Table 21e. Drug Interactions between the CCR5 Antagonist Maraviroc and Other Drugs (Including Antiretroviral Agents) (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 3)

Concomitant Drug Class/Name	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PIs, continued		
DRV/c, DRV/r	**With (DRV/r 600 mg/100 mg) Twice Daily:** • MVC AUC ↑ 305% **With (DRV/r 600 mg/100 mg) Twice Daily and ETR:** • MVC AUC ↑ 210%	MVC 150 mg twice daily
LPV/r	MVC AUC ↑ 295% **With LPV/r and EFV:** • MVC AUC ↑ 153%	MVC 150 mg twice daily
TPV/r	**With (TPV/r 500 mg/200 mg) Twice Daily:** • ↔ MVC AUC	No dose adjustment needed.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV/r = tipranavir/ritonavir

Table 22a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 2)

Note: Interactions associated with DLV, FPV, IDV, NFV, and SQV are **not** included in this table. Please refer to the FDA product labels for information regarding interactions between these drugs and other concomitant drugs.

PIs		NNRTIs				
		DOR	**EFV**	**ETR**	**NVP**	**RPV**
ATV Unboosted	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ↔ ATV AUC and C_{min} ↓ 47%	↑ NVP possible ↓ ATV possible	↑ RPV possible ↔ ATV expected
	Dose	No dose adjustment needed.	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	No dose adjustment needed.
ATV/c	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV expected ↓ ATV possible ↓ COBI possible	↑ ETR possible ↓ ATV possible ↓ COBI possible	↑ NVP possible ↓ ATV possible ↓ COBI possible	↑ RPV possible ↔ ATV expected
	Dose	No dose adjustment needed.	**ATV/c in ART-Naive Patients:** • ATV 400 mg plus COBI 150 mg once daily • **Do not use coformulated ATV 300 mg/ COBI 150 mg.** **ATV/c in ART-Experienced Patients:** • **Do not coadminister.** No dose adjustment needed for EFV.	**Do not coadminister.**	**Do not coadminister.**	No dose adjustment needed.
ATV/r	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV expected **(ATV 400 mg plus RTV 100 mg) Once Daily:** • ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV	**(ATV 300 mg plus RTV 100 mg) Once Daily:** • ETR AUC and C_{min} both ↑ ~30% • ↔ ATV AUC and C_{min}	**(ATV 300 mg plus RTV 100 mg) Once Daily:** • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible ↔ ATV expected
	Dose	No dose adjustment needed.	**ATV/r in ART-Naive Patients:** • (ATV 400 mg plus RTV 100 mg) once daily **ATV/r in ART-Experienced Patients:** • **Do not coadminister.** No dose adjustment needed for EFV.	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.
DRV/c	**PK Data**	↑ DOR expected ↔ DRV expected	↔ EFV expected ↓ DRV possible ↓ COBI possible	**ETR 400 mg Once Daily with (DRV 800 mg plus COBI 150 mg) Once Daily:** • ↔ ETR AUC and C_{min} • ↔ DRV AUC and C_{min} ↓ 56% • COBI AUC ↓ 30% and C_{min} ↓ 66%	↑ NVP possible ↓ DRV possible ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	No dose adjustment needed.	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	No dose adjustment needed.

Table 22a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 2)

PIs		NNRTIs				
		DOR	EFV	ETR	NVP	RPV
DRV/r	**PK Data**	↑ DOR expected ↔ DRV expected	**With (DRV 300 mg plus RTV 100 mg) Twice Daily:** • EFV AUC ↑ 21% • ↔ DRV AUC and C_{min} ↓ 31%	**ETR 100 mg Twice Daily with (DRV 600 mg plus RTV 100 mg) Twice Daily:** • ETR AUC ↓ 37% and C_{min} ↓ 49% • ↔ DRV	**With (DRV 400 mg plus RTV 100 mg) Twice Daily:** • NVP AUC ↑ 27% and C_{min} ↑ 47% • DRV AUC ↑ 24%[a]	**RPV 150 mg Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily:** • RPV AUC ↑ 130% and C_{min} ↑ 178% • ↔ DRV
	Dose	No dose adjustment needed.	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	No dose adjustment needed. Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	No dose adjustment needed.	No dose adjustment needed.
LPV/r	**PK Data**	↑ DOR expected ↔ LPV expected	↔ EFV expected **With LPV/r 500 mg/125 mg[b] Twice Daily:** • LPV concentration similar to that of LPV/r 400 mg/100 mg twice daily without EFV	ETR AUC ↓ 35% (comparable to the decrease seen with DRV/r) ↔ LPV AUC	↑ NVP possible LPV AUC ↓ 27% and C_{min} ↓ 51%	**RPV 150 mg Once Daily with LPV/r:** • RPV AUC ↑ 52% and C_{min} ↑ 74% • ↔ LPV
	Dose	No dose adjustment needed.	LPV/r 500 mg/125 mg[b] twice daily LPV/r 533 mg/133 mg twice daily when using oral solution No dose adjustment needed for EFV.	No dose adjustment needed.	LPV/r 500 mg/125 mg[b] twice daily LPV/r 533 mg/133 mg twice daily when using oral solution No dose adjustment needed for NVP.	No dose adjustment needed.
TPV/r **Note:** Always use TPV with RTV	**PK Data**	↑ DOR expected ↔ TPV expected	**With (TPV 500 mg plus RTV 100 mg) Twice Daily:** • ↔ EFV • TPV AUC ↓ 31% and C_{min} ↓ 42% **With (TPV 750 mg plus RTV 200 mg) Twice Daily:** • ↔ EFV and TPV	**With (TPV 500 mg plus RTV 200 mg) Twice Daily:** • ETR AUC ↓ 76% and C_{min} ↓ 82% • ↔ TPV AUC and C_{min} ↑ 24%	**With (TPV 250 mg plus RTV 200 mg) Twice Daily *or* with (TPV 750 mg plus RTV 100 mg) Twice Daily:** • ↔ NVP • ↔ TPV expected	↑ RPV possible ↔ TPV expected
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.	No dose adjustment needed.

[a] DRV concentration was compared to a historic control.

[b] Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

Key to Symbols: ↑ = increase ↓ = decrease ↔ = no change

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{min} = minimum plasma concentration; COBI = cobicistat; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Table 22b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 4)

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs					
DOR	**PK Data**	↔ DOR and BIC expected	↔ DOR DTG AUC ↑ 36% and C_{min} ↑ 27%	↑ DOR expected ↔ EVG	↔ DOR and RAL expected
	Dose	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.	No dose adjustment needed.
EFV	**PK Data**	↓ BIC expected	**With DTG 50 mg Once Daily:** • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, and EFV possible	**With RAL 400 mg Twice Daily:** • RAL AUC ↓ 36% and C_{min} ↓ 21% **With RAL 1,200 mg Once Daily:** • ↔ RAL AUC and C_{min}
	Dose	**Do not coadminister.**	**In Patients Without INSTI Resistance:** • DTG 50 mg twice daily **In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance:** • Consider alternative combination.	**Do not coadminister.**	No dose adjustment needed.
ETR	**PK Data**	↓ BIC expected	**ETR 200 mg Twice Daily plus DTG 50 mg Once Daily:** • DTG AUC ↓ 71% and C_{min} ↓ 88% **ETR 200 mg Twice Daily with (DRV 600 mg plus RTV 100 mg) Twice Daily and DTG 50 mg Once Daily:** • DTG AUC ↓ 25% and C_{min} ↓ 37% **ETR 200 mg Twice Daily with (LPV 400 mg plus RTV 100 mg) Twice Daily and DTG 50 mg Once Daily:** • DTG AUC ↑ 11% and C_{min} ↑ 28%	↑ or ↓ EVG, COBI, and ETR possible	**ETR 200 mg Twice Daily plus RAL 400 mg Twice Daily:** • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%

Table 22b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 4)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs, continued					
ETR	**Dose**	**Do not coadminister.**	**Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.** **In Patients Without INSTI Resistance:** • DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) **In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance:** • DTG 50 mg twice daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	RAL 400 mg twice daily **Coadministration with RAL 1,200 mg once daily is not recommended.**
NVP	**PK Data**	↓ BIC expected	**With DTG 50 mg Once Daily:** • DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, and NVP possible	No data
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.
RPV	**PK Data**	No data	**With DTG 50 mg Once Daily:** • ↔ DTG AUC and C_{min} ↑ 22% • ↔ RPV AUC and C_{min} ↑ 21%	↑ or ↓ EVG, COBI, and RPV possible	↔ RPV RAL C_{min} ↑ 27%
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.
PIs					
ATV	**PK Data**	**ATV 400 mg Once Daily plus BIC 75 mg Single Dose:** • BIC AUC ↑ 315%	**(ATV 400 mg plus DTG 30 mg) Once Daily:** • DTG AUC ↑ 91% and C_{min} ↑ 180%	↑ or ↓ EVG, COBI, and ATV possible	No data
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister.**	No dose adjustment needed.
ATV/c	**PK Data**	BIC AUC ↑ 306%	No data	Not applicable	No data
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister two COBI-containing products.**	No dose adjustment needed.

Table 22b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 4)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
PIs, continued					
ATV/r	**PK Data**	↑ BIC expected	**(ATV 300 mg plus RTV 100 mg) Once Daily plus DTG 30 mg Once Daily:** • DTG AUC ↑ 62% and C_{min} ↑ 121%	Not applicable	**With Unboosted ATV:** • RAL AUC ↑ 72% **With Unboosted ATV and RAL 1,200 mg:** • RAL AUC ↑ 67% **With (ATV 300 mg plus RTV 100 mg) Once Daily:** • RAL AUC ↑ 41%
	Dose	**Do not coadminister.**	No dose adjustment needed.	**Do not coadminister RTV and COBI.**	No dose adjustment needed.
DRV	**PK Data**	Not applicable	Not applicable	↔ DRV or EVG expected	Not applicable
	Dose	**Do not administer DRV without RTV or COBI.**	**Do not administer DRV without RTV or COBI.**	No dose adjustment needed.	**Do not administer DRV without RTV or COBI.**
DRV/c	**PK Data**	BIC AUC ↑ 74%	**DRV/c plus DTG Once Daily:** • ↔ DTG, DRV, and COBI **DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c:** • DTG C_{min} ↑ 100%	Not applicable	No data
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister two COBI-containing products.**	No dose adjustment needed.
DRV/r	**PK Data**	No data	**(DRV 600 mg plus RTV 100 mg) Twice Daily with DTG 30 mg Once Daily:** • DTG AUC ↓ 22% and C_{min} ↓ 38%	Not applicable	**With (DRV 600 mg plus RTV 100 mg) Twice Daily:** • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	No dose adjustment needed.	No dose adjustment needed.	**Do not coadminister RTV and COBI.**	No dose adjustment needed.
LPV/r	**PK Data**	No data	**With (LPV 400 mg plus RTV 100 mg) Twice Daily and DTG 30 mg Once Daily:** • ↔ DTG	Not applicable	↓ RAL ↔ LPV/r
	Dose	Consider alternative combination.	No dose adjustment needed.	**Do not coadminister RTV and COBI.**	No dose adjustment needed.
TPV/r	**PK Data**	↓ BIC possible	**With (TPV 500 mg plus RTV 200 mg) Twice Daily and DTG 50 mg Once Daily:** • DTG AUC ↓ 59% and C_{min} ↓ 76%	Not applicable	**With (TPV 500 mg plus RTV 200 mg) Twice Daily and RAL 400 mg Twice Daily:** • RAL AUC ↓ 24% and C_{min} ↓ 55%

Table 22b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 4)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
PIs, continued					
TPV/r	**Dose**	**Do not coadminister.**	**In Patients Without INSTI Resistance:** • DTG 50 mg twice daily **In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance:** • Consider alternative combination.	**Do not coadminister RTV and COBI.**	RAL 400 mg twice daily **Coadministration with RAL 1,200 mg once daily is not recommended.**

[a] Refer to DTG product label for details.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; C_{min} = minimum plasma concentration; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

Conclusion (Last updated January 28, 2016; last reviewed January 28, 2016)

The Panel has carefully reviewed results from clinical HIV therapy trials and considered how they affect appropriate care guidelines. HIV care is complex and rapidly evolving. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. Absent such evidence, the Panel has attempted to base recommendations on reasonable options for HIV care.

HIV care requires partnerships and open communication. Guidelines are only a starting point for medical decision making involving informed providers and patients. Although guidelines can identify some parameters of high-quality care, they cannot substitute for sound clinical judgment.

As further research is conducted and reported, these guidelines will be modified. The Panel anticipates continued progress in refining antiretroviral therapy regimens and strategies. The Panel hopes these guidelines are useful and is committed to their continued revision and improvement.

Appendix A: Key to Acronyms (Last updated July 10, 2019; last reviewed July 10, 2019)

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
BIC	bictegravir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ADAP	AIDS drug assistance program

Ag/Ab	antigen/antibody
Al	aluminum
ALT	alanine aminotransferase
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AUD	alcohol use disorder
AV	atrioventricular
AWP	average wholesale price
BID	twice daily
BMD	bone mineral density
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAA	direct-acting antiviral
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DMPA	depot medroxyprogesterone acetate

DOT	directly observed therapy
EBV	Epstein-Barr virus
EC	enteric coated
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FI	fusion inhibitor
FUL	federal upper limit
GAHT	gender-affirming hormone therapy
GAZT	azidothymidine glucuronide
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
HAD	HIV-associated dementia
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO_3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV RNA	HIV viral load
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HRT	hormone replacement therapy
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
K	potassium

KS	Kaposi's sarcoma
LDL	low-density lipoprotein
LLOD	lower limits of detection
MAC	*Mycobacterium avium* complex
MAT	medication-assisted treatment
MATE	multidrug and toxin extrusion transporter
MDMA	methylenedioxymethamphetamine
Mg	magnesium
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
msec	millisecond
MSM	men who have sex with men
MTR	multi-tablet regimen
Na	sodium
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OAT	opioid agonist therapy
OATP	organic anion-transporting polypeptide
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
ONDCP	Office of National Drug Control Policy
OR	odds ratio
OTP	opioid treatment program
OUD	opioid use disorder
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PI	protease inhibitor
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
PO	orally
PPI	proton pump inhibitor
PR	protease
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone

q(n)d	every (n) days
q(n)h	every (n) hours
QTc	QT corrected for heart rate
RNA	ribonucleic acid
RR	relative risk
RT	reverse transcriptase
SAMHSA	Substance Abuse and Mental Health Services Administration
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
STR	single-tablet regimen
SUD	substance use disorder
TB	tuberculosis
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
UGT	uridine diphosphate glucuronosyltransferase
VPA	valproic acid
WAC	wholesale acquisition cost
WHO	World Health Organization
XR	extended release
Zn	zinc

Appendix B, Table 1. Coformulated Single-Tablet Regimens (Last updated July 10, 2019; last reviewed December 18, 2019)

The following table includes dose recommendations for FDA-approved STR products. Please see the class-specific drug characteristics tables (Appendix B, Tables 3 to 6) for details about the individual drugs included in these STR products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The STR products in this table are listed by drug class and arranged **in alphabetical order** by trade name within each class.

Trade Name (Abbreviations)	ARV Drugs Included in the STR	Dosing Recommendation[a]
INSTI plus Two NRTIs		
Biktarvy (BIC/TAF/FTC)	Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily
Genvoya (EVG/c/TAF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet once daily with food
Stribild (EVG/c/TDF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily with food
Triumeq (DTG/ABC/3TC)	Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg	One tablet once daily
INSTI plus One NRTI		
Dovato (DTG/3TC)	Dolutegravir 50 mg/lamivudine 300 mg	One tablet once daily
PI plus Two NRTIs		
Symtuza (DRV/c/TAF/FTC)	Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet once daily with food
NNRTI plus Two NRTIs		
Atripla (EFV/TDF/FTC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily on an empty stomach, preferably at bedtime
Complera (RPV/TDF/FTC)	Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily with a meal
Delstrigo (DOR/TDF/3TC)	Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Odefsey (RPV/TAF/FTC)	Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily with a meal
Symfi (EFV/TDF/3TC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily on an empty stomach, preferably at bedtime
Symfi Lo (EFV/TDF/3TC)	Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily on an empty stomach, preferably at bedtime
INSTI plus One NNRTI		
Juluca (DTG/RPV)	Dolutegravir 50 mg/rilpivirine 25 mg	One tablet once daily with a meal

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the STR can be taken with or without food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 2. Nucleoside Reverse Transcriptase Inhibitor-Based, Fixed-Dose Combination Tablets for Use as Part of an Antiretroviral Regimen (Last updated July 10, 2019; last reviewed December 18, 2019)

The following table includes dose recommendations for FDA-approved, dual-NRTI FDC products. These FDC tablets **are not complete regimens** and must be administered in combination with other ARV drugs.

Please see the class-specific drug characteristics tables (Appendix B, Tables 3 to 6) for details about the individual drugs contained in these FDC products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. The FDC tablets in this table are listed by trade name.

Trade Name (Abbreviations)	ARV Drugs Included in the FDC Tablet	Dosing Recommendation[a]
TAF or TDF plus an NRTI		
Descovy (TAF/FTC)	Tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily
Cimduo (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Temixys (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Truvada (TDF/FTC)	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily
Other NRTI-Based, FDC Tablets		
Epzicom (ABC/3TC) **Note:** Generic product is available.	Abacavir 600 mg/lamivudine 300 mg	One tablet once daily
Combivir (ZDV/3TC) **Note:** Generic product is available.	Zidovudine 300 mg/lamivudine 150 mg	One tablet twice daily

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. All FDC tablets listed in this table can be taken without regard to food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 4)

The older NRTIs ddI and d4T are no longer commonly used in clinical practice and have been removed from this table. Please refer to the July 10, 2019, version of the guidelines (found in the archived guidelines section of AIDS*info*) or to the FDA product labels for ddI and d4T for information regarding these drugs.

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic tablet formulation is available.	**Ziagen:** • 300 mg tablet • 20 mg/mL oral solution **Generic:** • 300 mg tablet • Also available as FDC with 3TC and ZDV/3TC **FDC Tablets that Contain ABC:[c]** • Epzicom (ABC/3TC) • Trizivir (ABC/ZDV/3TC) **STRs that Contain ABC:[d]** • Triumeq (DTG/ABC/3TC)	**Ziagen**: • ABC 600 mg once daily, *or* • ABC 300 mg twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain ABC.	Metabolized by alcohol dehydrogenase and glucuronyl transferase 82% of ABC dose is excreted renally as metabolites Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 10).	1.5 hours/12–26 hours	Patients who test positive for HLA-B*5701 are at the highest risk of experiencing HSRs. HLA screening should be done before initiating ABC. For patients with a history of HSRs, rechallenge **is not recommended**. Symptoms of HSRs may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (e.g., sore throat, cough, or shortness of breath). Some cohort studies suggest an increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Emtricitabine (FTC) *Emtriva*	**Emtriva:** • 200 mg hard gelatin capsule • 10 mg/mL oral solution **FDC Tablets that Contain FTC:[c]** • Descovy (TAF/FTC) • Truvada (TDF/FTC) **STRs that Contain FTC:[d]** • Atripla (EFV/TDF/FTC) • Biktarvy (BIC/TAF/FTC) • Complera (RPV/TDF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Stribild (EVG/c/TDF/FTC) • Symtuza (DRV/c/TAF/FTC)	**Emtriva** *Capsule:* • FTC 200 mg once daily *Oral Solution:* • FTC 240 mg (24 mL) once daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain FTC.	86% of FTC dose is excreted renally See Appendix B, Table 10 for dosing recommendations in patients with renal insufficiency.	10 hours/>20 hours	Minimal toxicity Hyperpigmentation/skin discoloration Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue FTC.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic products are available.	**Epivir:** • 150 and 300 mg tablets • 10 mg/mL oral solution **Generic:** • 150 and 300 mg tablets • Also available as FDC with ABC and ZDV **FDC Tablets that Contain 3TC:[c]** • Cimduo (TDF/3TC) • Combivir (ZDV/3TC) • Epzicom (ABC/3TC) • Temixys (TDF/3TC) • Trizivir (ABC/ZDV/3TC) **STRs that Contain 3TC:[d]** • Delstrigo (DOR/TDF/3TC) • Dovato (DTG/3TC) • Symfi (EFV 600 mg/ TDF/3TC) • Symfi Lo (EFV 400 mg/ TDF/3TC) • Triumeq (DTG/ABC/3TC)	**Epivir:** • 3TC 300 mg once daily, *or* • 3TC 150 mg twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain 3TC.	70% of 3TC dose is excreted renally See Appendix B, Table 10 for dose recommendations in patients with renal insufficiency.	5–7 hours/18–22 hours	Minimal toxicity Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue 3TC.
Tenofovir Alafenamide (TAF) *Vemlidy* **Note:** Vemlidy is available as a 25-mg tablet for the treatment of HBV.	**FDC Tablets that Contain TAF:[c]** • Descovy (TAF/FTC) **STRs that Contain TAF:[d]** • Biktarvy (BIC/TAF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Symtuza (DRV/c/TAF/FTC)	See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TAF.	Metabolized by cathepsin A. See Appendix B, Table 10 for dosing recommendations in patients with renal insufficiency.	0.5 hours/150–180 hours	Renal insufficiency, Fanconi syndrome, and proximal renal tubulopathy are less likely to occur with TAF than with TDF. Osteomalacia and decreases in BMD are less likely to occur with TAF than with TDF. Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TAF. Diarrhea, nausea, headache

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Note:** Generic product is available.	**Viread:** • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder **Generic:** • 300 mg tablet **FDC Tablets that Contain TDF:**[c] • Cimduo (TDF/3TC) • Temixys (TDF/3TC) • Truvada (TDF/FTC) **STRs that Contain TDF:**[d] • Atripla (EFV/TDF/FTC) • Complera (RPV/TDF/FTC) • Delstrigo (DOR/TDF/3TC) • Stribild (EVG/c/TDF/FTC) • Symfi (EFV 600 mg/ TDF/3TC) • Symfi Lo (EFV 400 mg/ TDF/3TC)	**Viread:** • TDF 300 mg once daily, *or* • 7.5 level scoops of oral powder once daily (dosing scoop dispensed with each bottle; one level scoop contains 1 g of oral powder). Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.** See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TDF.	Renal excretion is the primary route of elimination. See Appendix B, Table 10 for dose recommendations in patients with renal insufficiency.	17 hours/>60 hours	Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy Osteomalacia, decrease in BMD Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TDF. Asthenia, headache, diarrhea, nausea, vomiting, flatulence
Zidovudine (ZDV) *Retrovir* **Note:** Generic products are available.	**Retrovir:** • 100 mg capsule • 10 mg/mL IV solution • 10 mg/mL oral solution **Generic:** • 300 mg tablet • Also available as FDC with 3TC and 3TC/ABC **FDC Tablets that Contain ZDV:**[c] • Combivir (ZDV/3TC) • Trizivir (ABC/ZDV/3TC)	**Retrovir:** • ZDV 300 mg twice daily, *or* • ZDV 200 mg three times a day See Appendix B, Table 2 for dosing information for FDC tablets that contain ZDV.	Metabolized to GAZT Renal excretion of GAZT See Appendix B, Table 10 for dosing recommendations in patients with renal insufficiency.	1.1 hours/ 7 hours	Macrocytic anemia Neutropenia Nausea, vomiting, headache, insomnia, asthenia Nail pigmentation Lactic acidosis/severe hepatomegaly with hepatic steatosis (this is a rare, but potentially life-threatening, toxicity) Hyperlipidemia Insulin resistance/diabetes mellitus Lipoatrophy Myopathy

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 4)

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 2 for information about these formulations.

[d] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BMD = bone mineral density; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FDA = Food and Drug Administration; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IV = intravenous; MI = myocardial infarction; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization; ZDV = zidovudine

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 2)

The older NNRTI DLV is no longer commonly used in clinical practice and is **not** listed this table. Please refer to the FDA product label for DLV for information regarding this drug.

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Doravirine (DOR) *Pifeltro*	**Pifeltro:** • 100 mg tablet Also available as part of the STR Delstrigo (DOR/TDF/3TC)[c]	**Pifeltro:** • One tablet once daily See Appendix B, Table 1 for dosing information for Delstrigo.	CYP3A4/5 substrate	15 hours	Nausea Dizziness Abnormal dreams
Efavirenz (EFV) *Sustiva* **Note:** Generic product is available.	**Sustiva:** • 50 and 200 mg capsules • 600 mg tablet **Generic:** • 600 mg tablet **STRs that Contain EFV:**[c] • Atripla (EFV/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	**Sustiva:** • EFV 600 mg once daily, at or before bedtime Take on an empty stomach to reduce side effects. See Appendix B, Table 1 for dosing information for STRs that contain EFV.	Metabolized by CYP2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2B6 and 2C19 inducer	40–55 hours	Rash[d] Neuropsychiatric symptoms[e] Serum transaminase elevations Hyperlipidemia Use of EFV may lead to false-positive results with some cannabinoid and benzodiazepine screening assays. QT interval prolongation
Etravirine (ETR) *Intelence*	**Intelence:** • 25, 100, and 200 mg tablets	**Intelence:** • ETR 200 mg twice daily Take following a meal.	CYP3A4, 2C9, and 2C19 substrate CYP3A4 inducer CYP2C9 and 2C19 inhibitor	41 hours	Rash, including Stevens-Johnson syndrome[d] HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure), have been reported. Nausea

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 2)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Nevirapine (NVP) *Viramune or Viramune XR* **Note:** Generic products are available.	**Viramune:** • 200 mg tablet • 50 mg/5 mL oral suspension **Viramune XR:** • 400 mg tablet **Generic:** • 200 mg tablet • 400 mg extended release tablet • 50 mg/5 mL oral suspension	**Viramune:** • NVP 200 mg once daily for 14 days (lead-in period); thereafter, NVP 200 mg twice daily, *or* • NVP 400 mg (Viramune XR tablet) once daily Take without regard to meals. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in dose until rash resolves, but do not extend lead-in period beyond 28 days total.	CYP450 substrate CYP3A4 and 2B6 inducer **Contraindicated** in patients with moderate to severe hepatic impairment. Dose adjustment is recommended in patients on hemodialysis (see Appendix B, Table 10).	25–30 hours	Rash, including Stevens-Johnson syndrome[d] **Symptomatic Hepatitis:** • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported. • Rash has been reported in approximately 50% of cases. • Symptomatic hepatitis occurs at a significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/mm^3. • NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.
Rilpivirine (RPV) *Edurant*	**Edurant:** • 25 mg tablet **STRs that Contain RPV:**[c] • Complera (RPV/TDF/FTC) • Juluca (DTG/RPV) • Odefsey (RPV/TAF/FTC)	**Edurant:** • RPV 25 mg once daily Take with a meal. See Appendix B, Table 1 for dosing information for STRs that contain RPV.	CYP3A4 substrate	50 hours	Rash[d] Depression, insomnia, headache Hepatotoxicity QT interval prolongation

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 1 for information about these formulations.

[d] Rare cases of Stevens-Johnson syndrome have been reported with the use of most NNRTIs; the highest incidence of rash was seen among patients who were receiving NVP.

[e] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (e.g., suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients who are receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks, but discontinuation of EFV may be necessary in a small percentage of patients. Late-onset neurotoxicities, including ataxia and encephalopathy, have been reported.

Key: 3TC = lamivudine; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FDC = fixed-dose combination; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 4)

The older PIs FPV, IDV, NFV, SQV, and TPV are no longer commonly used in clinical practice and have been removed from this table. Please refer to the July 10, 2019 version of the guidelines (found in the archived guidelines section of AIDS*info*) or to the FDA product labels for information regarding these drugs.

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Atazanavir (ATV) *Reyataz* (ATV/c) *Evotaz* **Note:** Generic products of ATV are available.	**Reyataz:** • 150, 200, and 300 mg capsules • 50 mg oral powder/packet **Generic:** • 100, 150, 200, and 300 mg capsules **Evotaz:** • ATV 300 mg/ COBI 150 mg tablet	**Reyataz** *In ARV-Naive Patients:* • (ATV 300 mg plus RTV 100 mg) once daily; *or* • ATV 400 mg once daily • Take with food. *With TDF or in ARV-Experienced Patients:* • (ATV 300 mg plus RTV 100 mg) once daily • Unboosted ATV **is not recommended**. • Take with food. *With EFV in ARV-Naive Patients:* • (ATV 400 mg plus RTV 100 mg) once daily • Take with food. **Evotaz**: • One tablet once daily • Take with food. • The use of ATV/c **is not recommended** for patients who are taking TDF and who have baseline CrCl <70 mL/min (see Appendix B, Table 10 for the equation for calculating CrCl). For dosing recommendations for patients who are also receiving H2 antagonists and PPIs, refer to Table 21a.	**ATV:** • CYP3A4 inhibitor and substrate • Weak CYP2C8 inhibitor • UGT1A1 inhibitor **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 10).	7 hours	Indirect hyperbilirubinemia PR interval prolongation. First degree symptomatic AV block has been reported. Use with caution in patients who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation. Cholelithiasis Nephrolithiasis Renal insufficiency Serum transaminase elevations Hyperlipidemia (especially with RTV boosting) Skin rash Hyperglycemia Fat maldistribution An increase in serum creatinine may occur when ATV is administered with COBI.

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 4)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Darunavir (DRV) *Prezista* (DRV/c) *Prezcobix*	**Prezista**: • 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension **Prezcobix**: • DRV 800 mg/ COBI 150 mg tablet Also available as part of the STR Symtuza (DRV/c/ TAF/FTC)	**Prezista** *In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations:* • (DRV 800 mg plus RTV 100 mg) once daily • Take with food. *In ARV-Experienced Patients with One or More DRV Resistance Mutations:* • (DRV 600 mg plus RTV 100 mg) twice daily • Take with food. Unboosted DRV **is not recommended**. **Prezcobix:** • One tablet once daily • Take with food. • **Not recommended** for patients with one or more DRV resistance-associated mutations. • Coadministering Prezcobix and TDF **is not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 10 for the equation for calculating CrCl). See Appendix B, Table 1 for dosing information for Symtuza.	**DRV:** • CYP3A4 inhibitor and substrate • CYP2C9 inducer **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	15 hours when combined with RTV 7 hours when combined with COBI	**Skin Rash:** DRV has a sulfonamide moiety, however incidence and severity of rash are similar in those with or without a sulfonamide allergy; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia Serum transaminase elevation Hyperglycemia Fat maldistribution An increase in serum creatinine may occur when DRV is administered with COBI.

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 4)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra* **Note:** LPV is only available as a component of an FDC tablet that also contains RTV.	**Kaletra:** • LPV/r 200 mg/50 mg tablets • LPV/r 100 mg/25 mg tablets • LPV/r 400 mg/100 mg per 5 mL of oral solution. Oral solution contains 42% alcohol.	**Kaletra:** • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily. However, once-daily dosing **is not recommended** for patients with three or more LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, carbamazepine, phenytoin, or phenobarbital. *With EFV or NVP in PI-Naive or PI Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily (use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or* • LPV/r 533 mg/133 mg oral solution twice daily **Food Restrictions** *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	GI intolerance, nausea, vomiting, diarrhea Pancreatitis Asthenia Hyperlipidemia (especially hypertriglyceridemia) Serum transaminase elevation Hyperglycemia Insulin resistance/ diabetes mellitus Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia PR interval prolongation QT interval prolongation and Torsades de Pointes have been reported; however, causality could not be established.
Ritonavir (RTV) Norvir **Note:** Generic is available. Although RTV was initially developed as a PI for HIV treatment, RTV is currently used at a lower dose of 100 mg to 200 mg once or twice daily as a PK enhancer to increase the concentrations of other PIs.	**Norvir:** • 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution. Oral solution contains 43% alcohol. • 100 mg single packet oral powder Also available as part of the FDC tablet Kaletra (LPV/r)	**As a PK Booster (or Enhancer) for Other PIs:** • RTV 100–400 mg per day in one or two divided doses (refer to other PIs for specific dosing recommendations). **Food Restrictions** *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 > 2D6 substrate Potent CYP3A4 and 2D6 inhibitor Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	3–5 hours	GI intolerance, nausea, vomiting, diarrhea Paresthesia (circumoral and extremities) Hyperlipidemia (especially hypertriglyceridemia) Hepatitis Asthenia Taste perversion Hyperglycemia Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 4)

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10.

[b] Also see Table 17.

Key: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FDA = Food and Drug Administration; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronyl transferase

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Bictegravir (BIC)	BIC is only available as a component of the STR Biktarvy (BIC/TAF/FTC).[c]	**Biktarvy:** • One tablet PO once daily	CYP3A4 substrate UGT1A1-mediated glucuronidation	~17 hours	Diarrhea Nausea Headache Weight gain
Dolutegravir (DTG) *Tivicay*	**Tivicay:** • 50 mg tablet **STRs that Contain DTG:**[c] • Dovato (DTG/3TC) • Juluca (DTG/RPV) • Triumeq (DTG/ABC/3TC)	**In ARV-Naive or ARV-Experienced, INSTI-Naive Patients:** • DTG 50 mg PO once daily **In ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered with EFV, FPV/r, TPV/r, or Rifampin:** • DTG 50 PO mg twice daily **INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance:** • DTG 50 mg PO twice daily See Appendix B, Table 1 for dosing information for STRs that contain DTG.	UGT1A1-mediated glucuronidation Minor substrate of CYP3A4	~14 hours	Insomnia Headache Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions) Weight gain Hepatotoxicity There is a potential increased risk of NTDs in infants born to individuals who received DTG around the time of conception (see Table 6b for more information). HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury), have been reported.
Elvitegravir (EVG)	EVG is only available as a component of an STR tablet that also contains COBI, FTC, and either TDF or TAF. **STRs that Contain EVG:**[c] • Genvoya (EVG/c/TAF/FTC) • Stribild (EVG/c/TDF/FTC)	**Genvoya:** • One tablet PO once daily with food • See Appendix B, Table 10 for recommendations on dosing in persons with renal insufficiency. **Stribild:** • One tablet PO once daily with food • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 10 for the CrCl calculation equation).	**EVG:** • CYP3A and UGT1A1/3 substrate **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	**EVG/c:** ~13 hours	Nausea Diarrhea Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions)

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Raltegravir (RAL) *Isentress* *Isentress HD*	**Isentress:** • 400 mg tablet • 25 and 100 mg chewable tablets • 100 mg single-use packet for oral suspension **Isentress HD:** • 600 mg tablet	**Isentress** *In ARV-Naive Patients or ARV-Experienced Patients:* • 400 mg PO twice daily *With Rifampin:* • 800 mg twice daily **Isentress HD** *In ARV-Naive or ARV-Experienced Patients with Virologic Suppression on a Regimen containing RAL 400 mg Twice Daily:* • 1,200 mg (two 600-mg tablets) PO once daily *With Rifampin:* • **Not recommended**	UGT1A1-mediated glucuronidation	~9 hours	Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis Nausea Headache Diarrhea Pyrexia CPK elevation, muscle weakness, and rhabdomyolysis Weight gain Insomnia Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions)

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PO = orally; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate glucuronyl transferase

Appendix B, Table 7. Characteristics of the Fusion Inhibitor (Last updated December 18, 2019; last reviewed December 18, 2019)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Adverse Events[a]
Enfuvirtide (T-20) *Fuzeon*	**Fuzeon:** • Injectable; supplied as lyophilized powder. • Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. • Refer to prescribing information for storage instruction.	**Fuzeon:** • T-20 90 mg/1 mL SQ twice daily	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients Increased incidence of bacterial pneumonia HSR occurs in <1% of patients. Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. **Re-challenge is not recommended.**

[a] Also see Table 17.

Key: HSR = hypersensitivity reaction; SQ = subcutaneous; T-20 = enfuvirtide

Appendix B, Table 8. Characteristics of the CCR5 Antagonist (Last updated December 18, 2019; last reviewed December 18, 2019)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	**Selzentry:** • 150 and 300 mg tablets	**Selzentry:** • MVC 150 mg PO twice daily when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers), including PIs (except TPV/r) • MVC 300 mg PO twice daily when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg PO twice daily when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take MVC without regard to meals.	14–18 hours	CYP3A4 substrate	Abdominal pain Cough Dizziness Musculoskeletal symptoms Pyrexia Rash Upper respiratory tract infections Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions Orthostatic hypotension, especially in patients with severe renal insufficiency

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10.

[b] Also see Table 17.

Key: CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 9. Characteristics of the CD4 Post-Attachment Inhibitor (Last updated December 18, 2019; last reviewed December 18, 2019)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
Ibalizumab (IBA) *Trogarzo*	**Trogarzo:** • Single-dose 2 mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab	**Trogarzo:** • Administer a single loading dose of IBA 2,000 mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800 mg IV infusion over 15 minutes every 2 weeks. • See prescribing information for additional instructions for preparing, storing, and administering IBA, and for monitoring patients who are receiving IBA.	~64 hours	Not well defined	Diarrhea Dizziness Nausea Rash

Key: IBA = ibalizumab; IV = intravenous

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 6)

The older ARV drugs ddI, d4T, FPV, IDV, NFV, SQV, and TPV are no longer commonly used in clinical practice and have been removed from this table. Please refer to the July 10, 2019, guidelines in the Guidelines Archive section of AIDS*info* or to the FDA product labels for these drugs for recommendations on dosing in persons with renal or hepatic insufficiency.

See the reference section at the end of this table for CrCl calculation formulas and criteria for Child-Pugh classification.

<table>
<tr><th>Generic Name
(Abbreviations)
Trade Name</th><th>Usual Daily Dose[a]</th><th>Dosing in Persons with Renal Insufficiency</th><th>Dosing in Persons with Hepatic Impairment</th></tr>
<tr><td colspan="4">Some FDC products are not recommended in persons with different degrees of renal insufficiency. The recommendations for individual FDCs based on CrCl level are outlined below.
• CrCl <70 mL/min: Initiation of Stribild is not recommended.
• CrCl <50 mL/min: FDCs not recommended: Atripla, Combivir, Complera, Delstrigo, Dovato, Epzicom, Triumeq, or Trizivir.
• CrCl <30 mL/min: FDCs not recommended: Biktarvy and Truvada.
• CrCl <30 mL/min and not on HD: FDCs not recommended: Descovy, Genvoya, Odefsey, and Symtuza.
The component drugs in some of the FDC products listed above may be prescribed as individual formulations with dose adjustment based on CrCl level as indicated below in this table.</td></tr>
<tr><td colspan="4">NRTIs</td></tr>
<tr><td>Abacavir
(ABC)
Ziagen</td><td>ABC 300 mg PO twice daily
or
ABC 600 mg PO once daily</td><td>No dose adjustment necessary.</td><td>Child-Pugh Class A: ABC 200 mg PO twice daily (use oral solution)
Child-Pugh Class B or C:
Contraindicated</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>FTC 200 mg oral capsule once daily
or
FTC 240 mg (24 mL) oral solution once daily</td><td>Dose by Formulation
<table><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg every 48 hours</td><td>120 mg every 24 hours</td></tr><tr><td>15–29</td><td>200 mg every 72 hours</td><td>80 mg every 24 hours</td></tr><tr><td><15</td><td>200 mg every 96 hours</td><td>60 mg every 24 hours</td></tr><tr><td>On HD[b]</td><td>200 mg every 24 hours</td><td>240 mg every 24 hours</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Lamivudine
(3TC)
Epivir</td><td>3TC 300 mg PO once daily
or
3TC 150 mg PO twice daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg every 24 hours</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg every 24 hours</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg every 24 hours</td></tr><tr><td><5 or on HD[b]</td><td>1 x 50 mg, then 25 mg every 24 hours</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
<tr><td>Tenofovir Alafenamide
(TAF)
Vemlidy</td><td>Vemlidy is available as a 25-mg tablet for the treatment of HBV.</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td><15 and not on HD</td><td>Not recommended</td></tr><tr><td>On HD[b]</td><td>One tablet once daily.</td></tr></table></td><td>Child-Pugh Class B or C: Not recommended</td></tr>
</table>

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 6)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Persons with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
NRTIs, continued			
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	TAF for HIV treatment is only available as a component of FDC tablets (i.e., in Descovy, Genvoya, Odefsey, Biktarvy, and Symtuza). TAF 10 mg PO daily with EVG/c (Genvoya) or DRV/c (Symtuza) TAF 25 mg PO daily in other FDC tablets	**CrCl (mL/min)** / **Dose** <30 and not on HD: **Not recommended** <30 and on HD[b]: One tablet once daily.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Tenofovir Disoproxil Fumarate (TDF) *Viread*	TDF 300 mg PO once daily	**CrCl (mL/min)** / **Dose** 30–49: 300 mg every 48 hours 10–29: 300 mg twice weekly (every 72–96 hours) <10 and not on HD: No recommendation On HD[b]: 300 mg every 7 days	No dose adjustment necessary.
Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) *Truvada*	One tablet PO once daily	**CrCl (mL/min)** / **Dose** 30–49: One tablet every 48 hours <30 or on HD: **Not recommended**	No dose recommendation.
Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) *Cimduo*	One tablet PO once daily	**CrCl (mL/min)** / **Dose** <50 or on HD: **Not recommended**	No dose recommendation.
Zidovudine (ZDV) *Retrovir*	ZDV 300 mg PO twice daily	**CrCl (mL/min)** / **Dose** <15 or on HD[b]: 100 mg three times a day or 300 mg once daily	No dose recommendation.
NNRTIs			
Doravirine (DOR) *Pifeltro*	One tablet PO once daily	No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in individuals with ESRD or on HD.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Doravirine/Tenofovir Disoproxil Fumarate/ Lamivudine (DOR/TDF/3TC) *Delstrigo*	One tablet PO once daily	**Not recommended** if CrCl <50 mL/min.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 6)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Persons with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
NNRTIs, continued			
Efavirenz (EFV) *Sustiva*	EFV 600 mg PO once daily on an empty stomach, preferably at bedtime	No dose adjustment necessary.	No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	One tablet PO once daily on an empty stomach, preferably at bedtime	**Not recommended** if CrCl <50 mL/min. Instead, use the individual component ARVs and adjust TDF and FTC doses according to CrCl level.	No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz 600 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi*	One tablet once daily on an empty stomach, preferably at bedtime	**Not recommended** if CrCl <50 mL/min or if patient is on HD. Instead, use the individual component ARVs and adjust TDF and 3TC doses according to CrCl level.	**Not recommended** for patients with moderate or severe hepatic impairment. Use with caution in patients with mild hepatic impairment.
Efavirenz 400 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) *Symfi Lo*	One tablet once daily on an empty stomach, preferably at bedtime	**Not recommended** if CrCl <50 mL/min or if patient is on HD. Instead, use the individual component ARVs and adjust TDF and 3TC doses according to CrCl level.	**Not recommended** for patients with moderate or severe hepatic impairment. Use with caution in patients with mild hepatic impairment.
Etravirine (ETR) *Intelence*	ETR 200 mg PO twice daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	NVP 200 mg PO twice daily *or* NVP 400 mg PO once daily (using Viramune XR formulation)	No dose adjustment for patients with renal impairment. Patients on HD should receive an additional dose of NVP 200 mg following each dialysis treatment.	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B or C:* **Contraindicated**
Rilpivirine (RPV) *Edurant*	RPV 25 mg PO once daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine/Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	One tablet PO once daily	**In Patients on Chronic HD:** • One tablet once daily. On HD days, administer after dialysis. **Not recommended** in patients with CrCl <30 mL/min who are not receiving chronic HD.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	One tablet PO once daily	**Not recommended** if CrCl <50 mL/min. Instead, use the individual component ARVs and adjust TDF and FTC doses according to CrCl level.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 6)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Persons with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
NNRTIs, continued			
Rilpivirine/ Dolutegravir (RPV/DTG) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
PIs			
Atazanavir (ATV) *Reyataz*	ATV 400 mg PO once daily *or* (ATV 300 mg plus RTV 100 mg) PO once daily	No dose adjustment for patients with renal dysfunction who do not require HD. **In ARV-Naive Patients on HD:** • (ATV 300 mg plus RTV 100 mg) once daily **In ARV-Experienced Patients on HD:** • ATV and ATV/r **are not recommended**	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B:* ATV 300 mg once daily (unboosted) for ARV-naive patients only *Child-Pugh Class C:* **Not recommended** RTV boosting **is not recommended** in patients with hepatic impairment.
Atazanavir/Cobicistat (ATV/c) *Evotaz*	One tablet PO once daily	**If Used with TDF:** • **Not recommended** if CrCl <70 mL/min	**Not recommended** in patients with hepatic impairment.
Darunavir (DRV) *Prezista*	**In ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations:** • (DRV 800 mg plus RTV 100 mg) PO once daily with food **In ARV-Experienced Patients with at Least One DRV Resistance Mutation:** • (DRV 600 mg plus RTV 100 mg) PO twice daily	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Impairment:* No dose adjustment *In Patients with Severe Hepatic Impairment:* **Not recommended**
Darunavir/Cobicistat (DRV/c) *Prezcobix*	One tablet PO once daily	**If Used with TDF:** • **Not recommended** if CrCl <70 mL/min	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Darunavir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	One tablet PO once daily	**In Patients on Chronic HD:** • One tablet once daily. On HD days, administer after dialysis. **Not recommended** in patients with CrCl <30 mL/min who are not receiving chronic HD.	**Not recommended** for patients with severe hepatic impairment.

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 6)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Persons with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
PIs, continued			
Lopinavir/Ritonavir (LPV/r) *Kaletra*	(LPV/r 400 mg/100 mg) PO twice daily *or* (LPV/r 800 mg/200 mg) PO once daily	Avoid once-daily dosing in patients on HD.	No dose recommendation; use with caution in patients with hepatic impairment.
Ritonavir (RTV) *Norvir*	**As a PI-Boosting Agent:** • RTV 100–400 mg per day	No dose adjustment necessary.	Refer to recommendations for the primary (i.e., boosted) PI.
INSTIs			
Bictegravir/Tenofovir Alafenamide/ Emtricitabine (BIC/TAF/FTC) *Biktarvy*	One tablet once daily	**Not recommended** for use in patients with CrCl <30 mL/min.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir (DTG) *Tivicay*	DTG 50 mg once daily *or* DTG 50 mg twice daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir/ Abacavir/Lamivudine (DTG/ABC/3TC) *Triumeq*	One tablet once daily	**Not recommended** if CrCl <50 mL/min. Instead, use the individual component drugs and adjust 3TC dose according to CrCl.	*Child-Pugh Class A:* Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these patients. *Child-Pugh Class B or C:* **Contraindicated** due to the ABC component
Dolutegravir/ Rilpivirine (DTG/RPV) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Elvitegravir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	One tablet once daily	**In Patients on Chronic HD:** • One tablet once daily. On HD days, administer after dialysis. **Not recommended** in patients with CrCl <30 mL/min who are not receiving chronic HD.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* **Not recommended**
Elvitegravir/ Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine (EVG/c/TDF/FTC) *Stribild*	One tablet once daily	EVG/c/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* **Not recommended**

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Persons with Renal or Hepatic Insufficiency (Last updated December 18, 2019; last reviewed December 18, 2019) (page 6 of 6)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Persons with Renal Insufficiency	Dosing in Persons with Hepatic Impairment
INSTIs, continued			
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL 400 mg twice daily (using Isentress formulation) *or* RAL 1,200 mg once daily (using Isentress HD formulation only)	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* No recommendation
Fusion Inhibitor			
Enfuvirtide (T-20) *Fuzeon*	T-20 90 mg SQ twice daily	No dose adjustment necessary.	No dose adjustment necessary.
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 8 for detailed dosing information.	**In Patients with CrCl <30 mL/min or Patients Who Are on HD** *Without Potent CYP3A Inhibitors or Inducers:* • MVC 300 mg twice daily; if postural hypotension occurs, reduce to MVC 150 mg twice daily *With Potent CYP3A Inducers or Inhibitors:* • **Not recommended**	No dose recommendations. MVC concentrations will likely be increased in patients with hepatic impairment.
CD4 Post-Attachment Inhibitor			
Ibalizumab (IBA) *Trogarzo*	Loading dose: IBA 2,000 mg IV Maintenance dose: IBA 800 mg IV every 2 weeks	No dose adjustment recommended.	No recommendation.

[a] Refer to Appendix B, Tables 1–9 for additional dosing information.

[b] On dialysis days, the patient should take the dose after the HD session.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAPD = chronic ambulatory peritoneal dialysis; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; HD = hemodialysis; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; XR = extended release; ZDV = zidovudine

Creatinine Clearance Calculation			
Male:	$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	Female:	$\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total Bilirubin, *or*	<2 mg/dL (<34 µmol/L)	2–3 mg/dL (34–50 µmol/L)	>3 mg/dL (>50 µmol/L)
Modified Total Bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin Time (Seconds Prolonged), *or*	<4	4–6	>6
International Normalized Ratio (INR)	<1.7	1.7–2.3	>2.3

[a] **Encephalopathy Grades**

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir.

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score.

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EXHIBIT 58

EXHIBIT 59

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

NICHOLAS HARRISON and OUTSERVE-SLDN, INC., Plaintiffs, vs. JAMES N. MATTIS, In His Official Capacity As Secretary of Defense; MARK ESPER, In His Official Capacity As the Secretary of the Army; and the UNITED STATES DEPARTMENT OF DEFENSE, Defendants. No. 1:18-cv-00641 LMB-IDD

RICHARD ROE, VICTOR VOE, and and OUTSERVE-SLDN, INC., Plaintiffs, vs. JAMES N. MATTIS, In His Official Capacity As Secretary of Defense; HEATHER A. WILSON, In Her Official Capacity as Secretary of the AIR FORCE; and the UNITED STATES DEPARTMENT OF DEFENSE, Defendants. No. 1:18-cv-01565

VIDEOTAPED 30(b)(6) DEPOSITION OF
THE UNITED STATES AIR FORCE FOR THE ROE CASE
GIVEN BY MARTHA P. SOPER

DATE: Wednesday, March 6, 2019
TIME: 9:20 a.m.

LOCATION: Winston & Strawn
1700 K Street, N.W.
Washington, D.C.

REPORTED BY: Denise M. Brunet, RPR
Reporter/Notary

Veritext Legal Solutions
1250 Eye Street, N.W., Suite 350
Washington, D.C. 20005

A P P E A R A N C E S

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On behalf of the U.S. Department of Justice:

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(Appearances continued on the next page.)

APPEARANCES (continued):

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ALSO PRESENT: Solomon Francis, Videographer

C O N T E N T S

(Exhibits continued on the next page.)

SOPER DEPOSITION EXHIBITS: PAGE:

(*Exhibits attached to the transcript.)

HIV-related medical accession standards?

MR. NORWAY: Objection. Outside of scope. Objection. Calls for the disclosure of deliberative information, the discussions of a policy-making working group. I'll instruct the witness not to answer.

BY MR. SCHOETTES:

Q Are you going to follow advice of counsel not to answer the question?

A Yes, sir.

Q Is there a DODI instruction specifically relating to HIV?

MR. NORWAY: Objection. Outside of scope.

You may answer.

THE WITNESS: Yes.

BY MR. SCHOETTES:

Q What instruction is that, if you know?

A I believe, and I could be wrong, it's 6405.90.

Q Let me offer. Is it possibly 6485.01?

A Yes, sir, it could be that.

Q All right. Is AFI 44-178 the Air Force's policy implementing DODI 6485.01?

A Yes, I believe it is.

Q If you look to page 2 of the 2018 report, Exhibit 5, at the end of the first full paragraph there, it states, "As with all other disqualifying medical conditions, applicants may be considered for a medical waiver."

And this is in the context of, if you look to the page before, the accessions policy that that statement is made. Has a waiver for accession ever been granted to a person living with HIV into the Air Force? Let me rephrase that question.

Has the Air Force ever granted a waiver for accession to a person living with HIV?

A Not to my knowledge.

Q Do you know on average what percentage of Air Force accessions are permitted based on a medical waiver?

MR. NORWAY: Objection. Outside of scope.

You may answer if you know.

THE WITNESS: Not to my knowledge. I don't know.

BY MR. SCHOETTES:

Q What does it mean to be considered deployable with limitations?

A Deployable with limitations ensures that the airmen going to a -- tasked to go to a certain location has the required support needed, either medically or...

Q So if an individual is designated as deployable with limitations, what are the limitations that are placed on that person's ability to deploy?

MR. NORWAY: Objection. Form. Are you referencing any particular Air Force policy, Scott?

MR. SCHOETTES: No. I guess I want to know in general how this term is -- is used.

MR. NORWAY: So is your question how the Air Force uses the term "deployment with limitations"? Is that from a DOD policy?

MR. SCHOETTES: It is now in a DOD policy.

MR. NORWAY: Okay.

MR. SCHOETTES: But I'm trying to assess whether it has been used or applied even prior to the issuance of that particular DODI.

MR. NORWAY: Okay. Can you say your question again?

MR. SCHOETTES: Yes.

MR. NORWAY: I just have a follow-up question.

FURTHER EXAMINATION BY COUNSEL FOR THE U.S. DEPARTMENT OF JUSTICE

BY MR. NORWAY:

Q Ma'am, does the Air Force historically offer individuals who are going through the DES process an opportunity to retrain into a different career field?

A To my knowledge, historically, no.

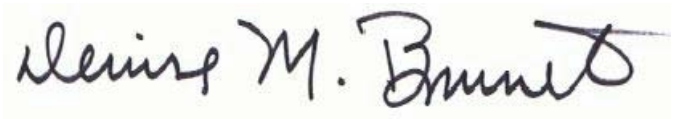
MR. NORWAY: Thank you very much.

THE VIDEOGRAPHER: The time is 7:31 p.m. This conclude today's testimony given by Ms. Martha P. Soper. We are now off the record.

(Whereupon, at 7:31 p.m., the deposition of MARTHA P. SOPER was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, Denise M. Brunet, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was sworn by me; that the testimony of said witness was taken by me stenographically and thereafter reduced to print by means of computer-assisted transcription by me to the best of my ability; that I am neither counsel for, related to, nor employed by any of the parties to this litigation and have no interest, financial or otherwise, in the outcome of this matter.



Denise M. Brunet
Notary Public in and for
The District of Columbia

My commission expires:
December 14, 2022

Veritext Legal Solutions
1100 Superior Ave
Suite 1820
Cleveland, Ohio 44114
Phone: 216-523-1313

March 15, 2019

To: Mr. Norway

Case Name: Roe, Richard, Et Al. v. Shanahan, Patrick M., Et Al.

Veritext Reference Number: 3235709

Witness: Martha P. Soper , 30(B)(6) Deposition Date: 3/6/2019

Dear Sir/Madam:

Enclosed please find a deposition transcript. Please have the witness review the transcript and note any changes or corrections on the included errata sheet, indicating the page, line number, change, and the reason for the change. Have the witness' signature notarized and forward the completed page(s) back to us at the Production address shown above, or email to production-midwest@veritext.com.

If the errata is not returned within thirty days of your receipt of this letter, the reading and signing will be deemed waived.

Sincerely,
Production Department

NO NOTARY REQUIRED IN CA

DEPOSITION REVIEW
CERTIFICATION OF WITNESS

ASSIGNMENT REFERENCE NO: 3235709
CASE NAME: Roe, Richard, Et Al. v. Shanahan, Patrick M., Et Al.
DATE OF DEPOSITION: 3/6/2019
WITNESS' NAME: Martha P. Soper , 30(B)(6)

In accordance with the Rules of Civil Procedure, I have read the entire transcript of my testimony or it has been read to me.

I have made no changes to the testimony as transcribed by the court reporter.

_____ _____
Date Martha P. Soper , 30(B)(6)

Sworn to and subscribed before me, a Notary Public in and for the State and County, the referenced witness did personally appear and acknowledge that:

They have read the transcript;
They signed the foregoing Sworn Statement; and
Their execution of this Statement is of their free act and deed.

I have affixed my name and official seal

this _____ day of_____, 20____.

_____
Notary Public

_____
Commission Expiration Date

DEPOSITION REVIEW
CERTIFICATION OF WITNESS

ASSIGNMENT REFERENCE NO: 3235709
CASE NAME: Roe, Richard, Et Al. v. Shanahan, Patrick M., Et Al.
DATE OF DEPOSITION: 3/6/2019
WITNESS' NAME: Martha P. Soper , 30(B)(6)

In accordance with the Rules of Civil Procedure, I have read the entire transcript of my testimony or it has been read to me.

I have listed my changes on the attached Errata Sheet, listing page and line numbers as well as the reason(s) for the change(s).

I request that these changes be entered as part of the record of my testimony.

I have executed the Errata Sheet, as well as this Certificate, and request and authorize that both be appended to the transcript of my testimony and be incorporated therein.

_____ _____
Date Martha P. Soper , 30(B)(6)

Sworn to and subscribed before me, a Notary Public in and for the State and County, the referenced witness did personally appear and acknowledge that:

They have read the transcript;
They have listed all of their corrections in the appended Errata Sheet;
They signed the foregoing Sworn Statement; and
Their execution of this Statement is of their free act and deed.

I have affixed my name and official seal this _____ day of_____, 20____.

_____
Notary Public

_____
Commission Expiration Date

ERRATA SHEET

VERITEXT LEGAL SOLUTIONS MIDWEST

ASSIGNMENT NO: 3/6/2019

PAGE/LINE(S) / CHANGE /REASON

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_____ _____

Date Martha P. Soper , 30(B)(6)

SUBSCRIBED AND SWORN TO BEFORE ME THIS _____

DAY OF _____, 20_____ .

_____

Notary Public

_____

Commission Expiration Date

FILED UNDER SEAL
EXHIBIT 60