# EXHIBIT 44

## Excerpts from the May 10, 2019 Deposition of Craig Walter Hendrix, M.D.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

- - - - - - - - - - - - - - - - - -x
NICHOLAS HARRISON, et al., :
Plaintiffs, :
vs. : Case No.
PATRICK M. SHANAHAN, et al., : 1:18-cv-641-LMB-IDD
Defendants. :
- - - - - - - - - - - - - - - - - -x
RICHARD ROE, et al., :
Plaintiffs, :
vs. : Case No.
PATRICK M. SHANAHAN, et al., : 1:18-cv-1565-LMB-IDD
Defendants. :
- - - - - - - - - - - - - - - - - -x

Washington, D.C.
Friday, May 10, 2019

Deposition of CRAIG WALTER HENDRIX, M.D., a witness herein, called for examination by counsel for the Defendants in the above-entitled matter, pursuant to notice, the witness being duly sworn by KAREN YOUNG, a Notary Public in and for the District of Columbia, taken at the offices of Winston & Strawn

Q. Okay, and I'm going to actually direct you to the box that's on page 2 because it's easier to do that. So -- and in this article, the authors say that in order for antiretroviral therapy to provide maximum benefit, taking medications as prescribed is essential, correct?

A. That's what it says.

Q. Okay. Do you agree with that?

A. Yes.

Q. Does the validity of the U versus U concept depend on achieving and maintaining an undetectable viral load?

A. Yes.

Q. Yes, and is taking antiretroviral medications as prescribed essential for maintaining -- achieving and maintaining an undetectable viral load?

A. Largely. The only -- the only qualifier is that taking it as prescribed may not mean perfection because there is also evidence that suppression is complete even if there's a small degree of nonadherence, but adherence needs to be good.

Q. Okay. What do you mean by a small degree of nonadherence?

A. So it would -- specifically it would be an

occasional missed dose at a frequency of, say, you know, one -- one a week roughly, like 85 percent -- if 85 percent adherence is maintained in a consistent way, which is on average, it's like missing a dose a week, I don't think there's evidence that there would -- I think there is evidence that there would not be a loss of full suppression. There's other patterns of nonadherence that may not have that impact.

Q. Let's talk about the other patterns of nonadherence. So what -- your answer to my last question involved essentially one missed dose a week, correct? Is -- is as prescribed -- let me -- let me see if I can frame the question. If there is a pattern of nonadherence of two missed doses a week back to back, does that reduce or -- the validity of the U versus U concept?

A. So I think 85 sticks in my head, so two would be -- you know, one minus 28 is more than that. I would be concerned at that level for treatment and full suppression.

Q. Okay. So you would also be concerned if --

A. Right.

Q. -- if they missed three --

A. In terms of full suppression at some point in time.

Q. Okay, at some point in time.
A. At some point in time, yes.
Q. And if they take a dose, then is your concern lessened?
MR. SCHOETTES: Objection, vague.
BY MR. NORWAY:
Q. Let me -- let me -- so after -- after the individual has missed two doses in a row, if they took a third dose, would your concern be less? Never mind. It's a bad question. It's a bad question. So in the -- in the -- in the context of U versus U, in your opinion, you become concerned once an individual misses two doses in a row?
MR. SCHOETTES: Objection, mischaracterizes prior testimony and vague. You may answer.
A. So I'll just repeat what I said before. I'm comfortable with data -- I can't think of the author and the journal, but I'm comfortable with data that adherence can be 85 percent -- I think that's in general. I added an opinion, not -- based on principles and other data, but not a study that was done in a way to see if there was a -- a week holiday, for example, but there is no increased risk because the viral load is not going to be changing much in that week. That's not a good thing. I don't

want it to continue, but that's also -- if I'm off for a week, I'm exceeding this 15 percent tolerance.

Q. Okay.

A. That makes -- it's very complicated. I'm -- I'm happy to say 85 percent is going to be really good at maintaining full viral suppression.

Q. Yeah, and what I'm -- what I'm asking is in your opinion, how long after a person stops taking their medication do you become concerned that they may transmit HIV.

MR. SCHOETTES: You can answer that.

A. So -- so the two important things there would be at what point -- the critical thing is at what -- how much later are they not suppressed, so how long's it take for them to get from fully suppressed, which is below whatever number, depending on the test, to something that's going to be over, say, 400, you know, 200, 400 based on the Quinn papers. Some of these other papers here, they use different numbers, and that period of time I think is -- I think the range on average is four to ten or 12 weeks.

So until that point in time, I would have a -- I wouldn't be so worried that there's an issue because they would maintain -- it takes the virus a

UNITED STATES OF AMERICA )

ss:

DISTRICT OF COLUMBIA )

I, KAREN YOUNG, a Notary Public within and for the District of Columbia, do hereby certify that the witness whose deposition is hereinbefore set forth was duly sworn and that the within transcript is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 22nd day of May, 2019.

Karen Young

My Commission Expires:

July 31, 2019

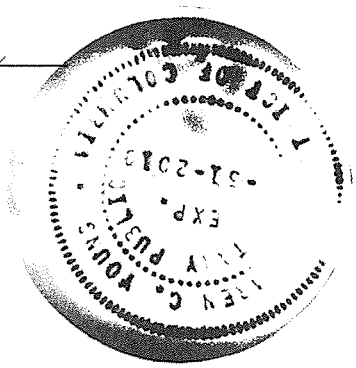

Exhibit 12 to Deposition of Dr. Craig Hendrix

# Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

October 2018

AIDSinfo

# Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV



Downloaded from https://aidsinfo.nih.gov/guidelines on 5/6/2019

# 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 October 25, 2018; last reviewed October 25, 2018)

## Resistance Testing

New information has been added regarding the use of HIV-1 proviral DNA genotypic resistance tests to identify drug resistance mutations, especially in the setting of low-level viremia or when plasma HIV RNA is below the limit of detection. The section now includes a discussion on the benefits and limitations of these tests.

## Co-Receptor Tropism Testing

For patients who have undetectable HIV RNA, the Panel now recommends using a proviral DNA tropism assay to assess co-receptor usage before maraviroc is initiated as part of a new regimen.

## Dolutegravir and Association with Neural Tube Defects

Preliminary data from Botswana suggest that there is an increased risk of neural tube defects in infants born to women who were receiving dolutegravir (DTG) at the time of conception. In response to these preliminary data, several sections in the Adult and Adolescent Guidelines have been updated to provide guidance for clinicians who are considering the use of DTG or other integrase strand transfer inhibitors (INSTIs) in individuals who are pregnant, or in those of childbearing potential who plan to get pregnant or who are sexually active and not using effective contraception. The sections that have been updated with this new information include:

- What to Start
- Virologic Failure
- Optimizing Antiretroviral Therapy in the Setting of Viral Suppression (formerly Regimen Switching in the Setting of Virologic Suppression)
- Acute and Recent (Early) HIV-1 Infection
- Adolescents and Young Adults with HIV
- Women with HIV

## What to Start

The following changes have been made to the recommendations for initial antiretroviral (ARV) regimens:

- **Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC):** BIC is a new INSTI that is approved by the Food and Drug Administration (FDA) as part of a single-tablet regimen (STR) that also includes TAF and FTC. This regimen is now classified as a Recommended Initial Regimen for Most People with HIV.
- **Elvitegravir/Cobicistat/Emtricitabine with Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate (EVG/c/FTC/TAF or EVG/c/FTC/TDF):** These regimens have been moved to the category of Recommended Initial Regimens in Certain Clinical Situations. This change was made because these combinations include cobicistat, a pharmaco-enhancer that inhibits cytochrome P450 3A4 and increases the likelihood of drug-drug interactions. EVG also has a lower barrier to resistance than DTG and BIC.
- **Doravirine (DOR):** DOR, a new non-nucleoside reverse transcriptase inhibitor, was recently approved by the FDA and is available as a single-drug tablet and as part of an STR that also includes TDF

and lamivudine (3TC). DOR/TDF/3TC and DOR plus TAF/FTC have been added to the category of Recommended Initial Regimens in Certain Clinical Situations.

- **Dolutegravir plus Lamivudine (DTG plus 3TC):** This two-drug regimen is now one of the regimens to consider when abacavir, TAF, or TDF cannot be used or are not optimal.
- A new table, Table 6b, has been added to provide guidance to clinicians who are considering the use of DTG or other INSTIs in those who are pregnant and in those of childbearing potential.
- Several new tables (Tables 8a–8d) have been added to the sections for the individual drug classes. These tables compare the characteristics of the different drugs within the classes.
- Updates have been made throughout the section with new safety and clinical trial data.

## Virologic Failure

- This section was updated to include newly reported data and new language on recently published clinical trial data for first-line ARV treatment failure.
- The Panel notes that, in some persons with multidrug-resistant HIV, DTG may be the only treatment option, or one of few treatment options. Accordingly, the language on the use of DTG in those of childbearing potential has been updated. The section now emphasizes that clinicians and patients should discuss the risk of neural tube defects if pregnancy occurs while the patient is taking DTG, as well as the risk of persistent viremia in the patient and the risk of HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ARV therapy. The decision of whether to initiate or continue DTG should be made after carefully considering these risks.
- Ibalizumab (IBA), a CD4 post-attachment inhibitor, was recently approved for use in persons with multidrug-resistant HIV. A review of the results of a clinical trial on IBA use in this setting has been added to the section.

## Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

- The title of this section has been changed from **Regimen Switching in the Setting of Virologic Suppression** to **Optimizing Antiretroviral Therapy in the Setting of Viral Suppression** to better reflect the rationale for regimen changes in this setting.
- The Panel emphasizes the importance of reviewing all available resistance test results when constructing a new regimen.
- The role of HIV-1 proviral DNA genotypic resistance testing in detecting archived drug resistance mutations in the setting of viral suppression is discussed.
- The Panel recommends performing pregnancy testing for those of childbearing potential before a regimen switch and provides recommendations for INSTI use in these patients.
- Clinical trial data on the use of several ARV combinations in switch studies are updated and discussed in this section.

## Exposure-Response Relationship and Therapeutic Drug Monitoring Section

- This section has been removed from the guidelines.
- The subsection regarding the role of therapeutic drug monitoring in managing drug-drug interactions has been moved to the Drug-Drug Interactions section of the guidelines.

## Additional Updates

Various tables in the guidelines have been updated with new data, as well as information related to BIC and DOR.

- Hepatitis C Virus/HIV Coinfection
- Adverse Effects of Antiretroviral Agents
- Monthly Average Prices of Commonly Used Antiretroviral Drugs
- Drug-Drug Interactions
- Appendix B Tables: Characteristics of Antiretroviral Drugs and Antiretroviral Dosing Recommendations in Patients with Renal and Hepatic Insufficiency

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## *List of Tables*

# HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Members and Consultants (Last updated October 25, 2018; last reviewed October 25, 2018)

*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).*

## Panel Co-Chairs

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| Roy M. Gulick | Weill Cornell Medicine, New York, NY |
| H. Clifford Lane | National Institutes of Health, Bethesda, MD |

## Executive Secretary

| | |
|---|---|
| Alice K. Pau | National Institutes of Health, Bethesda, MD |

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| Adaora Adimora | University of North Carolina School of Medicine, Chapel Hill, NC |
| Allison Agwu | Johns Hopkins University, Baltimore, MD |
| Curt Beckwith | Alpert School of Medicine, Brown University, Providence, RI |
| Roger Bedimo | University of Texas Southwestern & VA North Texas Health Care System, Dallas, TX |
| R. Douglas Bruce | Cornell Scott Hill Health Center, New Haven, CT |
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| Geetanjali Chander | Johns Hopkins University School of Medicine, Baltimore, MD |
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| Eric Daar | Harbor-UCLA Medical Center, Torrance, CA |
| Rajesh Gandhi | Massachusetts General Hospital & Harvard Medical School, Boston, MA |
| Stephen J. Gange | Johns Hopkins University, Baltimore, MD |
| Edward Gardner | Denver Public Health & University of Colorado, Denver, CO |
| Thomas Giordano | Baylor College of Medicine & Michael E. DeBakey VA Medical Center Houston, TX |
| David Glidden | University of California San Francisco, San Francisco, CA |
| Peter Hunt | University of California San Francisco, San Francisco, CA |
| Steven Johnson | University of Colorado School of Medicine, Aurora, CO |
| Rami Kantor | Alpert School of Medicine, Brown University, Providence, RI |
| Marla J. Keller | Albert Einstein College of Medicine & Montefiore Medical Center, Bronx, NY |
| Michael Kozal | Yale School of Medicine & VA Connecticut Healthcare System, New Haven, CT |
| Jeffrey Lennox | Emory University, Atlanta, GA |
| Susanna Naggie | Duke University, Durham, NC |
| Tonia Poteat | University of North Carolina School of Medicine, Chapel Hill, NC |
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| Susan Swindells | University of Nebraska Medical Center, Omaha, NE |
| Pablo Tebas | University of Pennsylvania, Philadelphia, PA |
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## Community Members

| | |
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| Danielle Campbell | Los Angeles Women's HIV/AIDS Task Force, Los Angeles, CA |
| David Evans | Project Inform, Pasadena, CA |
| Tim Horn | National Alliance of State and Territorial AIDS Directors, Washington, DC |
| Andy Kaytes | AIDS Treatment Activists Coalition, San Diego, CA |
| Steven Vargas | Association for the Advancement of Mexican Americans, Houston, TX |

## Members Representing Department of Health and Human Services Agencies

| | |
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| John T. Brooks | Centers for Disease Control and Prevention, Atlanta, GA |
| Laura Cheever | Health Resources and Services Administration, Rockville, MD |
| Henry Masur | National Institutes of Health, Bethesda, MD |
| Virginia Sheikh | Food and Drug Administration, Silver Spring, MD |
| Kimberly Struble | Food and Drug Administration, Silver Spring, MD |

## Non-Voting Observers

| | |
|---|---|
| Nahida Chakhtoura | National Institutes of Health, Bethesda, MD |
| Rohan Hazra | National Institutes of Health, Bethesda, MD |
| Safia Kuriakose | Leidos Biomedical Research, Inc., in support of National Institute of Allergy and Infectious Diseases, National Institutes of Health, Frederick, MD |

## Pharmacology Consultants

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| Sarita Boyd | Food and Drug Administration, Silver Spring, MD |
| Lauren Cirrincione | University of Nebraska Medical Center, Omaha, NE |
| Safia Kuriakose | Leidos Biomedical Research, Inc., in support of National Institute of Allergy and Infectious Diseases, National Institutes of Health, Frederick, MD |

## Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2018 to February 2019) (page 1 of 2)

| Panel Member | Status | Company (Relationship) |
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| Judith Aberg | M | • Frontier Biotechnologies (Research Support)<br>• Gilead (Research Support)<br>• Janssen (Advisory Board)<br>• Merck (Advisory Board)<br>• ViiV (Advisory Board, Research Support) |
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| R. Douglas Bruce | M | None |
| Danielle Campbell | M | • Gilead (Advisory Board) |
| Geetanjali Chander | M | None |
| Laura Cheever | M | None |
| Susan Cu-Uvin | M | None |
| Eric Daar | M | • Gilead (Consultant, Research Support)<br>• Merck (Research Support)<br>• ViiV (Research Support) |
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| Rajesh Gandhi | M | • Gilead (Advisory Board)<br>• Merck (Advisory Board |
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| Edward Gardner | M | None |
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| Marla J. Keller | M | None |

## Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2018 to February 2019) (page 2 of 2)

| Panel Member | Status | Company (Relationship) |
|---|---|---|
| Michael Kozal | M | • Gilead*<br>• ViiV*<br>* Yale University receives grant support from these companies for studies where Dr. Kozal served or serves as PI. Dr. Kozal is an employee of the federal government and does not receive any financial support from these grants. |
| H. Clifford Lane | C | None |
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| James Raper | M | None |
| Daniel Reirden | M | None |
| Kimberly Scarsi | M | None |
| Virginia Sheikh | M | None |
| Serena Spudich | M | None |
| Kimberly Struble | M | None |
| Susan Swindells | M | • ViiV (Research Support) |
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| Phyllis Tien | M | • Merck (Research Support)<br>• Theratechnologies (Research Support) |
| Steven Vargas | M | • ViiV (Honoraria) |
| Rochelle Walensky | M | None |

**Key to Acronyms:** C = Co-Chair; ES = Executive Secretary; M = Member; PI = Principal Investigator

## Introduction (Last updated January 28, 2016; last reviewed January 28, 2016)

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. In addition, ART is highly effective at preventing HIV transmission.[1] However, only 55% of people with HIV in the United States have suppressed viral loads,[2] mostly resulting from undiagnosed HIV infection and failure to link or retain diagnosed patients 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 primary goal of the Panel is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARVs) 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 patients, ARV drugs or combinations to avoid, management of treatment failure, management of adverse effects and drug interactions, and special ART-related considerations in specific patient populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children 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., sexual maturity rating [SMR] IV and V). Clinicians should follow recommendations in the Pediatric Guidelines when initiating ART in adolescents at SMR III or lower.[3] For recommendations related to pre- (PrEP) and post- (PEP) HIV exposure prophylaxis for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention (CDC).[4]

These guidelines represent current knowledge regarding the use of ARVs. 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 particular drugs or indications, and the use of the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration (FDA)-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 at http://www.aidsinfo.nih.gov). However, the guidelines cannot always be updated apace with the rapid evolution of new data and 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 (IRB)-approved clinical trials.

## 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 agents (ARVs) for the treatment of HIV in adults and adolescents in the United States. |
| **Panel members** | The Panel is composed of approximately 45 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 Resource 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 in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to 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 for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf). |
| **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. 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) use for adults and adolescents with HIV. For more detailed discussion on the use of ART for children and prepubertal adolescents (SMR I – III), clinicians should refer to the Pediatric ARV Guidelines.<br><br>These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women. |
| **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 that may have an impact on the clinical care of patients. 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 (http://www.aidsinfo.nih.gov). |
| **Public comments** | A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received 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 upon scientific evidence and expert opinion. Each recommended 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 | 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 |

## *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., care for a larger panel of patients),[5-8] 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.

## References


1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at https://www.ncbi.nlm.nih.gov/pubmed/21767103.
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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 October 25, 2018; last reviewed October 25, 2018)

Several laboratory tests are important for initial evaluation of patients 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 the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations on the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are routinely used to monitor patients with HIV: CD4 T lymphocyte (CD4) cell count to assess immune function, and plasma HIV RNA (viral load) to assess level of HIV viremia. Resistance testing should be used to guide selection of an ARV regimen. 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. 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 Patients with HIV Before and After Initiation of Antiretroviral Therapy[a]** (page 1 of 3)

| 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 | √<br>If HIV diagnosis has not been confirmed | | | | | | | | |
| CD4 Count | √ | √ | | √<br>During first 2 years of ART, or if viremia develops while patient is on ART, or if CD4 count is <300 cells/mm³ | | √<br>After 2 Years on ART with Consistently Suppressed Viral Load:<br>*CD4 Count 300–500 cells/mm³:*<br>• Every 12 months<br>*CD4 Count >500 cells/mm³:*<br>• CD4 monitoring is optional. | √ | √ | √<br>Every 3–6 months |
| HIV Viral Load | √ | √ | √[d] | √[e] | √[e] | | √ | √ | Repeat testing is optional. |
| Resistance Testing | √ | √[f] | | | | | √ | √ | √[f] |
| HLA-B*5701 Testing | | √<br>If considering ABC | | | | | | | |

**Table 3. Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapy[a]** (page 2 of 3)

| 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] |
| **Tropism Testing** | | √<br>If considering a CCR5 antagonist | | | | | √<br>If considering a CCR5 antagonist, or for patients experiencing virologic failure on a CCR5 antagonist-based regimen | √ | |
| **Hepatitis B Serology** (HBsAb, HBsAg, HBcAb total)[g,h,i] | √ | √<br>May repeat if patient is nonimmune and does not have chronic HBV infection[h] | | | | √<br>May repeat if patient is nonimmune and does not have chronic HBV infection[h] | | √<br>Including prior to starting HCV DAA (see HCV/HIV Coinfection) | |
| **Hepatitis C Screening** (HCV antibody or, if indicated, HCV RNA)[j] | √ | | | | | √<br>Repeat HCV screening for at-risk patients[k] | | √ | |
| **Basic Chemistry**[l,m] | √ | √ | √ | √ | | | | √ | √<br>Every 6–12 months |
| **ALT, AST, Total Bilirubin** | √ | √ | √ | √ | | | | √ | √<br>Every 6–12 months |
| **CBC with Differential** | √ | √ | √<br>If on ZDV | √<br>If on ZDV or if CD4 testing is done | √ | | | √ | √<br>Every 3–6 months |

**Table 3. Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapy[a]** (page 3 of 3)

| 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] |
| Fasting Lipid Profile[n] | √ | √ | | | √ If abnormal at last measurement | √ If normal at last measurement | | √ | √ If normal at baseline, annually |
| Fasting Glucose or Hemoglobin A1C | √ | √ | | √ If abnormal at last measurement | | √ If normal at last measurement | | √ | √ If normal at baseline, annually |
| Urinalysis[m,o] | √ | √ | | | √ If on TAF or TDF[l] | √ | | √ | |
| Pregnancy Test[p] | √ | √ | | | | | | √ | |

[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 initiation occurs 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 to 8 weeks, repeat testing every 4 to 8 weeks until viral load is suppressed to <200 copies/mL. Thereafter, repeat testing every 3 to 6 months.

[e] In patients on ART, viral load typically is measured every 3 to 4 months. 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, 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; therefore, resistance testing should not be performed. 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.

[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 Infections 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 for confirmation. If the HBV viral load is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If negative, the patient should be vaccinated. Refer to the HIV Primary Care Guidelines and the Adult

and Adolescent Opportunistic Infections Guidelines for more detailed recommendations.[1,2]

[l] 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.

[l] Serum Na, K, $HCO_3$, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or 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] Consult the National Lipid Association's recommendations for management of patients with dyslipidemia.[4]

[o] Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

[p] This applies to people of childbearing potential.

**Key to Acronyms:** 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; 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; 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 Response 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)**<br>If ART initiation is deferred, repeat before initiating ART **(AIII)**.<br>In patients not initiating ART, repeat testing is optional **(CIII)**. | At entry into care **(AI)**<br>If ART is deferred, every 3 to 6 months[c] **(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[b] **(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.[8,39-45] 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:<br>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:<br>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).<br>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:<br>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:<br>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:<br>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:<br>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 October 17, 2017; last reviewed October 17, 2017)

**Panel's Recommendations**

- Antiretroviral therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection **(AI)**.
- ART is also recommended for individuals with HIV to prevent HIV transmission **(AI)**.
- When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

***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

Without antiretroviral therapy (ART), most individuals with HIV will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death. The primary goal of ART is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication to sustain plasma HIV-1 RNA (viral load) below limits of quantification by 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 prolongs life.

Furthermore, high plasma HIV-1 RNA is a major risk factor for HIV transmission; effective ART can reduce both viremia and transmission of HIV to sexual partners.[1,2] Modelling studies suggest that expanded use of ART may lower incidence and, eventually, prevalence of HIV on a community or population level.[3] Thus, a secondary goal of ART is to reduce the risk of HIV transmission.

Historically, individuals with HIV have had low CD4 counts at presentation to care.[4] However, there have been concerted efforts to increase testing of at-risk individuals and to link individuals with HIV to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining and certain serious non-AIDS 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$^3$ never achieve CD4 counts >500 cells/mm$^3$ after up to 10 years on ART[5,6] and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.[5-7]

Two large, randomized controlled trials that addressed the optimal time to initiate ART—START[8] and TEMPRANO[9]—demonstrated approximately a 50% reduction in morbidity and mortality among individuals with HIV who had CD4 counts >500 cells/mm$^3$ and who were randomized to receive ART immediately versus delaying initiation of ART (described in more detail below). The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) therefore recommends immediate initiation of ART for all people living with HIV, regardless of CD4 count **(AI)**. Prompt initiation of ART is particularly important for patients with certain clinical conditions, as discussed below.

The decision to initiate ART should always include consideration of a patient's comorbid conditions and his or her willingness and readiness to initiate therapy. Thus, on a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible.

## Panel's Recommendations

ART is recommended for all individuals with HIV, regardless of CD4 cell count, to reduce the morbidity and

mortality associated with HIV infection **(AI)**. ART is also recommended for individuals with HIV to prevent HIV transmission **(AI)**. When initiating ART, it is important to educate patients about the benefits of ART, and to address barriers to adherence and recommend strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible. 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.

While ART is recommended for all patients, the following conditions increase the urgency to initiate therapy:

- Pregnancy (refer to the Perinatal Guidelines for more detailed recommendations on the management of pregnant women with HIV)[10]
- AIDS-defining conditions, including HIV-associated dementia (HAD) and AIDS-associated malignancies
- Acute opportunistic infections (OIs) (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm$^3$)
- HIV-associated nephropathy (HIVAN)
- Acute/early infection (see discussion in the Acute/Early Infection section)
- HIV/hepatitis B virus coinfection
- HIV/hepatitis C virus coinfection

### *Acute Opportunistic Infections and Malignancies*

In patients who have AIDS-associated opportunistic diseases for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy), improvement of immune function with ART may improve disease outcomes, thus ART should be started as soon as possible. For patients with mild to moderate cutaneous Kaposi's sarcoma (KS), prompt initiation of ART alone without chemotherapy has been associated with improvement of the KS lesions, even though initial transient progression of KS lesions as a manifestation of immune reconstitution inflammatory syndrome (IRIS) can also occur.[11] Similarly, although an IRIS-like presentation of non-Hodgkin's lymphoma after initiation of ART has been described,[12] greater ART-mediated viral suppression is also associated with longer survival among individuals undergoing treatment for AIDS lymphoma.[13] Drug interactions should be considered when selecting ART given the potential for significant interactions between chemotherapeutic agents and some antiretroviral drugs (particularly some non-nucleoside reverse transcriptase inhibitors [NNRTIs] and ritonavir- or cobicistat-boosted regimens). However, a diagnosis of malignancy should not delay initiation of ART nor should initiation of ART delay treatment for the malignancy.

In the setting of some OIs, such as cryptococcal and tuberculous meningitis, for which immediate ART may increase the risk of serious IRIS, a short delay before initiating ART may be warranted.[14-17] When ART is initiated in a patient with an intracranial infection, the patient should be closely monitored for signs and symptoms associated with IRIS. In the setting of other OIs, such as *Pneumocystis jirovecii* pneumonia, early initiation of ART is associated with increased survival;[18] therefore, ART should not be delayed.

In patients who have active non-meningeal tuberculosis, initiating ART during treatment for tuberculosis confers a significant survival advantage;[19-23] therefore, ART should be initiated as recommended in *Mycobacterium Tuberculosis* Disease with HIV Coinfection.

Clinicians should refer to the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[11] for more detailed discussion on when to initiate ART in the setting of a specific OI.

### *The Need for Early Diagnosis of HIV*

Fundamental to the earlier initiation of ART recommended in these guidelines is the assumption that HIV will be diagnosed early in the course of the disease. Unfortunately, in some patients, HIV infection is not diagnosed until the later stages of the disease. Despite the recommendations for routine, opt-out HIV screening in the health care setting regardless of perceptions about a patient's risk of infection[24] and the gradual increase in CD4 counts at first presentation to care, the median CD4 count of newly diagnosed patients remains below 350 cells/mm$^3$.[4] Diagnosis of HIV infection is delayed more often in nonwhites, those who use injection drugs, and older adults than in other populations, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[25-27] Therefore, to ensure that the current treatment guidelines have maximum impact, routine HIV screening per current Centers for Disease Control and Prevention recommendations is essential. It is also critical that all patients who receive an HIV diagnosis are educated about HIV disease and linked to care for full evaluation, follow-up, and management as soon as possible. Once patients are in care, focused effort is required to initiate ART and retain them in the health care system so that both the individuals with HIV and their sexual partners can fully benefit from early diagnosis and treatment (see Adherence to the Continuum of Care).

## Evidence Supporting Benefits of Antiretroviral Therapy to Prevent Morbidity and Mortality

Although observational studies had been inconsistent in defining the optimal time to initiate ART,[28-31] randomized controlled trials now definitively demonstrate that ART should be initiated in all patients with HIV, regardless of disease stage. The urgency to initiate ART is greatest for patients at lower CD4 counts, where the absolute risk of OIs, non-AIDS morbidity, and death is highest. Randomized controlled trials have long shown that ART improves survival and delays disease progression in patients with CD4 counts <200 cells/mm$^3$ and/or history of AIDS-defining conditions.[18,32] Additionally, a randomized controlled trial conducted in Haiti showed that patients who started ART with CD4 counts between 200 to 350 cells/mm$^3$ survived longer than those who deferred ART until their CD4 counts fell below 200 cells/mm$^3$.[33] Most recently, the published START and TEMPRANO trials provide the evidence for the Panel's recommendation to initiate ART in all patients regardless of CD4 cell count **(AI)**. The results of these two studies are summarized below.

The START trial is a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm$^3$ were randomized to initiate ART soon after randomization (immediate-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. When the randomized arms of the study were closed, the primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events/100 person-years) in the immediate ART arm and 96 participants (4.1%, or 1.38 events/100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART [95% confidence interval (CI), 0.30–0.62, $P < .001$]). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies. The majority (59%) of clinical events in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm$^3$, evidence for a benefit of immediate ART even before CD4 count declines below this threshold. Furthermore, the benefit of immediate ART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate ART for each category of clinical events, the benefit of immediate ART appeared to be particularly strong for AIDS events (HR 0.28, [95% CI, 0.15–0.50, $P < .001$]), tuberculosis (HR 0.29, [95% CI, 0.12–0.73, $P = .008$]), and malignancies (HR 0.36, [95% CI, 0.19 to 0.66; $P = .001$]). Importantly, immediate ART also significantly reduced the rate of pooled serious non-AIDS events (HR0.61, [95% CI, 0.38–0.97, $P = 0.04$]).[8]

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$^3$ were randomized

to either immediate ART or deferred ART (based on the national guidelines criteria for starting treatment); half of the participants in each group received isoniazid for prevention of tuberculosis 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 with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favor of early ART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART is beneficial in reducing the rate of these clinical events.[9]

The TEMPRANO and START trials had very similar estimates of the protective effect of immediate ART among individuals with HIV who had CD4 counts >500 cells/mm$^3$, further strengthening the Panel's recommendation that ART be initiated in all patients regardless of CD4 cell count.

### *Theoretical Continued Benefit of Early Antiretroviral Therapy Initiation Long After Viral Suppression is Achieved*

While the START and TEMPRANO studies demonstrated a clear benefit of immediate ART initiation in individuals with CD4 cell counts >500 cells/mm$^3$, it is plausible that the benefits of early ART initiation continue long after viral suppression is achieved. As detailed in the Poor CD4 Cell Recovery and Persistent Inflammation section, persistently low CD4 counts and abnormally high levels of immune activation and inflammation despite suppressive ART predict an increased risk of not only AIDS events, but also non-AIDS events including kidney disease, liver disease, cardiovascular disease, neurologic complications, and malignancies. Earlier ART initiation appears to increase the probability of restoring normal CD4 counts, a normal CD4/CD8 ratio, and lower levels of immune activation and inflammation.[34-39] Individuals initiating ART very early (i.e., during the first 6 months after infection) also appear to achieve lower immune activation levels and better immune function (as assessed by vaccine responsiveness) during ART-mediated viral suppression than those who delay therapy for a few years or more.[40-42] Thus, while these questions have yet to be addressed in definitive randomized controlled trials, earlier ART initiation may result in less residual immune dysfunction during treatment, which theoretically may result in reduced risk of disease for decades to come.

## Evidence Supporting the Use of Antiretroviral Therapy to Prevent HIV Transmission

### *Prevention of Sexual Transmission*

A number of investigations, including biological, ecological, and epidemiological studies and one randomized clinical trial, provide strong evidence that treatment of individuals with HIV can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.[43,44] Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viremia and risk of HIV transmission—when plasma HIV RNA levels are lower, transmission events are less common.[1,2]

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the partner with HIV was ART naive with a CD4 count of 350 to 550 cells/mm$^3$ at enrollment to compare the effect of immediate ART versus delayed therapy (not started until CD4 count <250 cells/mm$^3$) on HIV transmission to the partner who did not have HIV.[45] At study entry, 97% of the participants reported to be in a heterosexual monogamous relationship. All study participants were counseled on behavioral modification and condom use. The interim results reported 28 linked HIV transmission events during the study period, with only one event in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04; 95% CI, 0.01–0.27; $P < 0.001$). The final results of this study showed a sustained 93% reduction of HIV transmission within couples when the partner with HIV was taking ART as prescribed and viral load was suppressed.[2] Notably, there were only eight cases of HIV transmission within couples after the partner with HIV started ART; four transmissions occurred before the partner with HIV

was virologically suppressed and four other transmissions occurred during virologic failure. These results provide evidence that suppressive ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission.[1,46-48] HPTN 052 was conducted in heterosexual couples and not in populations at risk of HIV transmission via male-to-male sexual contact or needle sharing. In addition, in this clinical trial, adherence to ART was excellent. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to individuals who are at risk of transmitting HIV to sexual partners **(AI)**. Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen. Clinicians should also stress that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STIs.

### *Prevention of Perinatal Transmission*

As noted above, effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent perinatal transmission of HIV. Effective suppression of HIV replication is a key determinant in reducing perinatal transmission. In the setting of maternal viral load suppressed to <50 copies/mL near delivery, use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to 0.1% to 0.5%.[50,51] ART is thus recommended for all pregnant women with HIV, for both maternal health and for prevention of HIV transmission to the newborn. In ART-naive pregnant women ART should be initiated as soon as possible, with the goal of suppressing plasma viremia throughout pregnancy (see Perinatal Guidelines).

## Considerations When Initiating Antiretroviral Therapy

ART regimens for treatment-naive patients currently recommended in this guideline (see What to Start) can suppress and sustain viral loads below the level of quantification in most patients who adhere to their regimens. Most of the recommended regimens have low pill burden and are well tolerated. Once started on treatment, patients must continue ART indefinitely.

### *Optimizing Adherence and Retention in Care*

The key to successful ART in maintaining viral suppression is adherence to the prescribed regimen. Treatment failure and resultant emergence of drug resistance mutations may compromise future treatment options. While optimizing adherence and linkage to care 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.[52] In both the START[8] and TEMPRANO[9] trials, participants randomized to immediate ART achieved higher rates of viral suppression than those randomized to delayed ART. Nevertheless, it is important to discuss strategies to optimize adherence and retention in care with patients before ART initiation.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, active substance abuse, unstable housing, other 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. Nevertheless, clinicians are often inaccurate in predicting ART adherence and ART reduces morbidity and mortality even in patients with relatively poor adherence and established drug resistance. Thus, mental illness, substance abuse, 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 possibly the type of ART regimen to recommend (see What to Start).

### *Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis*

Since many individuals may fail to engage in care during the delay between 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 engagement in care and increase the proportion of individuals who achieve and maintain ART-mediated viral suppression. This strategy was recently tested in a randomized controlled trial of 377 individuals in South Africa who had recently received HIV diagnoses. Those randomized to receive immediate ART on the day of diagnosis were significantly more likely than those randomized to usual care (three to five additional visits with adherence counseling over 2 to 4 weeks prior to ART initiation) to be virally suppressed at 10 months (64% vs. 51%).[53] Similar improvements in both the proportion of participants retained in care achieving viral suppression and survival at the end of 1 year were recently reported in a randomized controlled trial of same-day ART initiation conducted in Haiti.[54] While there are many differences between the health care systems, structural barriers to engagement in care, and underlying HIV and TB epidemics in South Africa and Haiti that limit the generalizability of these findings to the United States, these studies suggested that same-day initiation of ART may be feasible and could potentially improve clinical outcomes. While no randomized controlled trials have been performed in the United States, a recent pilot study of 39 individuals in San Francisco suggested that initiating ART on the same day of HIV diagnosis might modestly shorten the time to achieving viral suppression.[55] It should be emphasized, however, that ART initiation on the same day of HIV diagnosis is resource-intensive, requiring "on-call" clinicians, nurses, social workers, and laboratory staff to coordinate the patient transportation, clinical evaluation, counseling, accelerated insurance coverage, required intake laboratory testing, and systems in place to assure linkage to ongoing care. As these resources may not be available in all settings and the long-term clinical benefits of same-day ART initiation have yet to be proven in the United States, this approach remains investigational.

## 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."[56,57] There are limited data on the role of ART in these individuals. Given the clear benefit of ART regardless of CD4 count from the START and TEMPRANO studies, delaying ART to see if a patient becomes an elite controller after initial diagnosis 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 clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications. Nonetheless, even elite controllers with normal CD4 counts also have evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS related diseases.[56,58-60] One observational study suggests that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[61] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[62] Whether this potential immunologic benefit of ART in elite controllers outweighs potential ART toxicity and results in clinical benefit is unclear. Unfortunately, randomized controlled trials to address this question are unlikely, 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 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. Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV 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 similar to those observed in adults. Historically, 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.[63] Because youth often face multiple 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 accepting and adhering to therapy. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support (see Adolescents with HIV).[64]

## Conclusion

The results of definitive randomized controlled trials support the Panel's recommendation to initiate ART to all individuals with HIV, regardless of CD4 cell count. Early diagnosis of HIV infection, followed by prompt ART initiation, has clear clinical benefits in reducing morbidity and mortality for patients with HIV and decreasing HIV transmission to their sexual partners. Although there are certain clinical and psychosocial factors that may occasionally necessitate a brief delay in ART, ART should be started as soon as possible. Clinicians should educate patients on the benefits and risks of ART and the importance of adherence.

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# What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated October 25, 2018; last reviewed October 25, 2018)

**Panel's 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).
- A pregnancy test should be performed for those of childbearing potential prior to the initiation of antiretroviral therapy **(AIII)**.
- 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[a]—only for patients who are HLA-B*5701 negative **(AI)**
  - Dolutegravir (DTG) plus tenofovir[b]/emtricitabine[a] **(AI)**
  - Raltegravir plus tenofovir[b]/emtricitabine[a] (**BI** for tenofovir disoproxil fumarate, **BII** for tenofovir alafenamide)
- Preliminary data have raised concerns about an increased risk of neural tube defects in infants born to people who were receiving DTG at the time of conception. Before prescribing DTG or another INSTI, please refer to Table 6b for specific recommendations on initiating these drugs as part of initial therapy.
- 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] Lamivudine may substitute for emtricitabine or vice versa.

[b] Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (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 post-attachment inhibitor. In addition, two drugs, ritonavir (RTV or r) and cobicistat (COBI or c) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of some ARV drugs (e.g., 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 (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 T lymphocyte (CD4) cell count increases in most persons with HIV.[1-3] Emerging data support the use of two-drug regimens, such as

dolutegravir (DTG) plus 3TC, when ABC, TDF, and TAF cannot be used or are not optimal (see the section below titled Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal).

### *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 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 the 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 new medication replaces an existing medication from the same class in patients who have achieved virologic suppression on an initial regimen. 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 is virologically suppressed and who is not experiencing any adverse effects on a regimen that is not listed in Table 6a need not necessarily change to a regimen that is in that 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 are not recommended as initial ARV. 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 1–7 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 8 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 the Adult and Adolescent Guidelines, there have been several important changes in the Panel's recommendations for initial therapy in people with HIV. Among these changes, the following deserve particular emphasis:

INSTI-Based Regimens as Initial Antiretroviral Therapy:

- Bictegravir (BIC)/TAF/FTC has been added to the category of Recommended Initial Regimens for Most People with HIV **(AI)**. This regimen was added based on data from randomized Phase 3 clinical trials that demonstrated that its efficacy, safety, and tolerability are similar to other regimens that are recommended for most people with HIV—namely, dolutegravir (DTG)/ABC/3TC and DTG plus TAF/FTC.[4,5]
- EVG/c/TDF/FTC and EVG/c/TAF/FTC **(BI)** have been moved from the category of Recommended Initial Regimens for Most People with HIV to the category of Recommended Initial Regimens in Certain Clinical Situations. This change was made because these combinations include COBI, a pharmacoenhancer that inhibits cytochrome P (CYP) 3A4 and increases the likelihood of drug-drug interactions. EVG also has a lower barrier to resistance than DTG and BIC.
- Clinicians should review Table 6b before prescribing an INSTI to a person of childbearing potential, as preliminary data suggest that there is an increased risk of neural tube defects (NTDs) in infants born to people who were receiving DTG at the time of conception.[6,7] Until more information is available:
  - A negative pregnancy test result should be documented prior to initiating DTG in antiretroviral therapy (ART)-naive individuals of childbearing potential.
  - DTG **is not recommended** for those who are pregnant and within 12 weeks post-conception.
  - DTG **is also not recommended** for those of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception.
  - For those who are using effective contraception, use of a DTG-based regimen can be considered after discussing the risks and benefits of this drug with the patient.
  - It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect). The chemical structure of BIC is similar to that of DTG. As there are no safety data for BIC use around the time of conception, similar considerations should be discussed with those of childbearing potential before using this drug.

NNRTI-Based Regimens as Initial Antiretroviral Therapy:

- The regimen of doravirine (DOR) plus TDF/3TC or TAF/FTC has been added to the category of Recommended Initial Regimens in Certain Clinical Situations. DOR is a new NNRTI that was recently approved for use in ART-naive individuals when administered with two NRTIs. DOR/TDF/3TC is coformulated as a single-tablet regimen (STR). Clinical trial data have shown that this regimen is noninferior to efavirenz (EFV)- and darunavir/ritonavir (DRV/r)-based regimens.[8,9] DOR compares

favorably to EFV and DRV/r in terms of side effects. DOR-based therapy has not been directly compared to INSTI-containing combinations for initial therapy. In patients starting their first ART regimen, treatment-emergent resistance to DOR has been observed.

- EFV 400 mg/TDF/3TC and EFV 600 mg/TDF/FTC are now available as generic STRs. In a randomized trial (ENCORE-1), EFV 400 mg/TDF/3TC and EFV 600 mg/TDF/3TC had similar virologic efficacy, though EFV 400 mg/TDF/3TC had fewer side effects. There are insufficient data regarding the use of EFV 400 mg/TDF/3TC in pregnancy or in people receiving rifampin to recommend its use in these situations. See the NNRTI section below for considerations regarding the use of these two single-pill regimens.

Protease Inhibitor-Based Regimens as Initial Antiretroviral Therapy:

- Boosted atazanavir (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, ATV/r plus ABC/3TC was less potent than ATV/r plus TDF/FTC in people with HIV RNA >100,000 copies/mL.[10] In a separate randomized trial, ATV/r was less well tolerated than DRV/r.[11]

Other Regimens When Abacavir, Tenofovir Alafenamide, or Tenofovir Disoproxil Fumarate Cannot be Used or Are Not Optimal:

- DTG plus 3TC is now recommended by the Panel when ABC, TAF, or TDF cannot be used or are not optimal. This is based on the results of two large Phase 3 randomized clinical trials: DTG plus 3TC was noninferior to DTG plus TDF/FTC in terms of virologic efficacy, and no drug resistance was seen in either treatment group.[12] Longer-term data are needed before this new two-drug regimen is recommended for most people with HIV.
- Other regimens that can be considered are DRV/r plus raltegravir (RAL), as long as a patient's plasma HIV RNA is <100,000 copies/mL and CD4 cell count is >200/mm$^3$, or DRV/r plus 3TC, although the data for this regimen are not as extensive as for other combinations.
- Lopinavir/ritonavir (LPV/r) plus 3TC is no longer recommended because of pill burden and poor tolerability.

Generic Antiretroviral Drugs:

- A growing number of generic ARV medications have been approved by the FDA since the last revision of these guidelines. In some situations, cost and access are among the 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[a] **(AI)—if HLA-B*5701 negative** |
| • DTG plus tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC) |
| • RAL[c] plus tenofovir[b]/FTC[a] (**BI** for TDF/FTC, **BII** for TAF/FTC) |
| **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/tenofovir[b]/FTC (**BI** for both TAF/FTC and TDF/FTC) |
| • RAL[c] plus ABC/3TC[a] **(CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL** |
| Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV) |
| • (DRV/c or DRV/r) plus tenofovir[b]/FTC[a] **(AI)** |
| • (ATV/c or ATV/r) plus tenofovir[b]/FTCa **(BI)** |
| • (DRV/c or DRV/r) plus ABC/3TC[a] —**if HLA-B*5701 negative (BII)** |
| NNRTI plus 2 NRTIs: |
| • DOR/TDF[b]/3TC **(BI)** or DOR plus TAF[b]/FTC **(BIII)** |
| • EFV plus TDF[b]/FTC[a] (**BI** for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, **BII** for EFV 600 mg plus TAF/FTC) |
| • RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm$^3$** |
| Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal: |
| • DTG plus 3TC **(BI)** |
| • DRV/r plus RAL BID **(CI)—if HIV RNA <100,000 copies/mL and CD4 cell 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* |

**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/ABC/3TC, EFV 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.

[a] 3TC may be substituted for FTC, or vice versa. ABC/3TC, TDF/3TC, TDF/FTC, and TAF/FTC are available as coformulated, two-NRTI tablets, and they are also available as part of various STRs. Cost, access, and availability of STR formulations are among the factors to consider when choosing between 3TC and FTC.

[b] TAF and TDF are two forms of tenofovir approved by the 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.

[c] RAL can be given as RAL 400 mg BID or RAL 1200 mg (two, 600-mg tablets) once daily.

**Table 6a. Recommended Antiretroviral Regimens for Initial Therapy** (page 2 of 2)

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BID = twice daily; 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; TDF = tenofovir disoproxil fumarate

**Table 6b. Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy**

Pregnancy testing should be performed in those of childbearing potential prior to initiation of ART **(AIII)**. Preliminary data suggest that there is an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception.[67]

Before Initiating DTG:

- Providers and people of childbearing potential should discuss the benefits and risks of using DTG, including the possible risk of NTDs; appropriate counseling should be provided so that the individual can make an informed decision about the use of this drug **(AIII)**.
- DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception **(AII)**; *or*
  - Who are of childbearing potential and planning to become pregnant **(AII)**; *or*
  - Who are of childbearing potential, sexually active, and not using effective contraception **(AIII)**.
- For those who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG use with the individual **(BIII)**.
- It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect).
- The chemical structure of BIC is similar to DTG. There are no safety data on the use of BIC around the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART **(AIII)**.
- In a person who is pregnant, BIC **is not recommended** because of insufficient safety data **(AIII)**.
- In a person who is pregnant, EVG/c **is also not recommended** because low EVG concentrations have been reported when this drug is given during the second and third trimesters **(AII)**.[11]
- Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States; however, data on RAL use during the first trimester is limited to fewer than 300 deliveries. As it is currently not known whether the association between DTG and NTDs represents a class effect, this potential risk should be discussed with people of childbearing potential who prefer an INSTI-containing 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*

**Key to Acronyms:** ART = antiretroviral therapy; BIC = bictegravir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; RAL = raltegravir

## Selecting an Initial Antiretroviral Regimen

For most patients, initial therapy should be with two NRTIs combined with an INSTI; in some individuals, a combination of an NNRTI or RTV- or COBI-boosted PI should be considered (see below).

### *Choosing Between an INSTI-, PI-, or NNRTI-Based Regimen*

The choice between an INSTI, PI, or NNRTI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, barrier to resistance, adverse effects profile, convenience, comorbidities, concomitant

medications, and the potential for drug-drug interactions (see Tables 7 and 9 for guidance). 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. 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-containing regimens and INSTI-containing regimens, the INSTI was better tolerated and caused fewer treatment discontinuations.[11,14,15]

Among the INSTI-based regimens, RAL-containing regimens have the longest clinical experience, and they have been shown to have durable virologic efficacy. However, these regimens have a higher pill burden than BIC- and DTG-containing regimens. RAL also has a lower barrier to resistance than BIC and DTG. In clinical trials of ART-naive patients who were receiving BIC- or DTG-based therapy, resistance has not been seen in patients experiencing virologic failure, and transmitted resistance is rare. Because of its high barrier to resistance, DTG may be considered for patients who must start ART before resistance test results are available (e.g., during acute HIV infection, and in the setting of certain opportunistic infections). BIC may also be effective in this setting, but there is less clinical experience with it than with DTG. BIC-based regimens have been shown to be noninferior to DTG-based regimens in clinical trials.[4,5] DTG **is not recommended** as initial therapy in those who are pregnant and within 12 weeks post-conception, or in those of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception. The safety of BIC use in individuals of childbearing potential who desire pregnancy is unknown.

In the category of Recommended Initial Regimens in Certain Clinical Situations, EVG-based regimens have the advantage of being available as STRs. However, these regimens have the potential disadvantages of a lower barrier to resistance than DTG or BIC and, importantly, a greater potential for drug interactions because EVG is combined with COBI, a strong CYP3A4 inhibitor. PK-enhanced, PI-based regimens are also effective in ART-naive patients, but, like EVG/c-based regimens, they also carry the same disadvantage of increased drug interaction potential. For those individuals in whom ART needs to begin urgently before resistance test results are available, boosted DRV may be an appropriate choice, as there is a low rate of transmitted PI resistance, it has a high barrier to resistance, and there is a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is now available as an STR. Boosted atazanavir has relatively few metabolic adverse effects in comparison to other boosted-PI regimens; however, in a randomized clinical trial, ATV/r had a higher rate of adverse effect-associated drug discontinuation than DRV/r or RAL.[11] In a substudy of this trial, and in a separate cohort study, ATV/r use was associated with slower progression of atherosclerosis, as measured by carotid artery intima medial thickness.[16,17] Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and lopinavir/ritonavir [LPV/r]) and an increased risk of cardiovascular events, while this association was not seen with ATV.[18-23] Further study is needed.

NNRTI-based regimens (which include DOR, EFV, or rilpivirine [RPV]) may be optimal choices 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 been reported with DOR. EFV has a long track record of widespread use and is considered safe in persons of childbearing potential, and its minimal PK interaction with rifamycins makes it an attractive option for patients who require concomitant treatment for tuberculosis (TB). Most EFV-based regimens have excellent virologic efficacy, 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. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA levels (>100,000 copies/mL) and low CD4 counts (<200 cells/mm$^3$). DOR is now approved for use in ART-naive individuals with HIV. It is available both as a single-drug pill to be used with two NRTIs and as part of an STR that also includes TDF/3TC. Both formulations are taken once daily without regard to food. In randomized trials, DOR was noninferior to both EFV and to DRV/r when either of these drugs were taken in combination with two NRTIs. DOR has CNS tolerability advantages over EFV and favorable lipid effects when compared

with both DRV/r and EFV. It also has fewer potential drug interactions than EFV or RPV, and, unlike RPV, virologic effects are not compromised in those with high HIV RNA levels and low CD4 cell counts.

In those patients who cannot safely be prescribed a combination regimen that contains two NRTIs, there are now several two-drug treatment options. DTG plus 3TC is an option when ABC, TAF, and TDF cannot be used or are not optimal. Two randomized trials that collectively enrolled >1,400 participants with baseline HIV RNA levels <500,000 copies/mL compared DTG plus 3TC to a three-drug regimen of DTG plus TDF/FTC. At week 48, DTG plus 3TC was noninferior to DTG plus TDF/FTC in terms of virologic efficacy. No treatment-emergent resistance was seen in either group.[12] Another option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination can only be used in those with baseline CD4 cell counts >200 cells/mm$^3$ and HIV RNA levels <100,000 copies/mL.[24] A small, randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to DRV/r plus TDF/3TC, although this study has yet to be published.[25]

### *Factors to Consider When Selecting an Initial Regimen*

When selecting a regimen for an individual person with HIV, a number of patient- and regimen-specific characteristics should be considered. The goal is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen for the patient in order to achieve sustained virologic control. Some of the factors to consider during regimen selection can be grouped into the categories listed below. Table 7 includes recommendations for 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 positive should not receive ABC.
- Individual preferences
- Anticipated adherence to the regimen

Specific Comorbidities or Other Conditions:

- Cardiovascular disease, hyperlipidemia, renal disease, liver disease, osteopenia/osteoporosis or conditions associated with bone mineral density (BMD) loss, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or those with the potential to become pregnant. Clinicians should refer to Table 6b and the latest Perinatal Guidelines for more detailed recommendations on the safety and effectiveness of ARV drugs during conception and throughout pregnancy.
- Coinfections: hepatitis B virus (HBV), hepatitis C virus (HCV), TB

Regimen-Specific Considerations:

- Regimen's barrier to resistance
- Potential adverse effects
- Known or potential drug interactions with other medications (see Drug-Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of fixed-dose combination (FDC) formulations, food requirements)
- Cost and access (see Cost Considerations and Antiretroviral Therapy)

**Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios** (page 1 of 4)

This table provides guidance to 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.

**Note:** Preliminary data suggest that there may be an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Until more information is available, clinicians should review Table 6b for further guidance before prescribing an INSTI to a person of childbearing potential.

| Patient or Regimen Characteristics | Clinical Scenario | Consideration(s) | Rationale/Comments |
|---|---|---|---|
| **Pre-ART Characteristics** | CD4 cell count <200 cells/mm³ | Do Not Use the Following Regimens:<br>• RPV-based regimens<br>• DRV/r plus RAL | A higher rate of virologic failure has been observed in those with low pretreatment CD4 cell counts. |
| | HIV RNA >100,000 copies/mL | Do Not Use the Following Regimens:<br>• RPV-based regimens<br>• ABC/3TC with EFV or ATV/r<br>• DRV/r plus RAL | Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels. |
| | 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 rapid initiation of ART is warranted | **Avoid NNRTI-based regimens.**<br>**Avoid ABC.**<br>Recommended ART Regimens:<br>• (DRV/r or DRV/c) plus tenofovir[a]/FTC<br>• DTG plus tenofovir[a]/FTC | Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.<br>HLA-B*5701 results may not be available rapidly.<br>Transmitted resistance to DRV and DTG is rare, and these drugs have high barriers to resistance.<br>Refer to Table 6b for further guidance before initiating DTG in persons of childbearing potential. |
| **ART-Specific Characteristics** | A 1-pill, once-daily regimen is desired | STR Options as Initial ART Include:<br>• BIC/TAF/FTC<br>• DOR/TDF/3TC<br>• DRV/c/TAF/FTC<br>• DTG/ABC/3TC<br>• EFV/TDF/FTC<br>• EFV/TDF/3TC<br>• EVG/c/TAF/FTC<br>• EVG/c/TDF/FTC<br>• RPV/TAF/FTC<br>• RPV/TDF/FTC | Do not use RPV-based regimens if HIV RNA is >100,000 copies/mL and CD4 cell count is <200/mm³.<br>Do not use DTG/ABC/3TC if patient is HLA-B*5701 positive.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.<br>See Appendix B, Table 8 for ARV dose recommendations in the setting of renal impairment. |
| | Food effects | Regimens that Can be Taken Without Regard to Food:<br>• BIC-, DOR-, DTG-, or RAL-based regimens | Oral bioavailability of these regimens is not significantly affected by food.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. |

**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, continued | Regimens that Should be Taken with Food:<br>• ATV/r- or ATV/c-based regimens<br>• DRV/r- or DRV/c-based regimens<br>• EVG/c/TAF/FTC[a]<br>• EVG/c/TDF/FTC[a]<br>• RPV-based regimens | Food improves absorption of these regimens. RPV-containing regimens should be taken with at least 390 calories of food. |
| | | Regimens that Should be Taken on an Empty Stomach:<br>• 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) | **Avoid TDF unless the patient has ESRD.** Use ABC or TAF.<br>ABC may be used if patient is HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).<br>TAF may be used if CrCl >30 mL/min.<br>Consider avoiding ATV.<br>ART Options When ABC, TAF or TDF Cannot be Used:<br>• DTG plus 3TC<br>• DRV/r plus 3TC<br>• DRV/r plus RAL (if CD4 cell 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.<br>An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 8 for specific dosing recommendations.<br>TAF has less impact on renal function and lower rates of proteinuria than TDF.<br>ATV has been associated with chronic kidney disease in some observational studies.<br>ABC has not been associated with renal dysfunction.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. |
| | 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 8 for specific dosing recommendations.<br>Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease. |
| | Osteoporosis | **Avoid TDF.**<br>Use ABC or TAF.<br>ABC may be used if patient is HLA-B*5701 negative. If HIV RNA >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 and ABC are associated with smaller declines in BMD than TDF. |
| | Psychiatric illnesses | **Consider avoiding EFV- and RPV-based regimens.**<br>Patients on INSTI-based regimens who have pre-existing psychiatric conditions should be closely monitored.<br>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.<br>INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series.<br>See the drug-drug interaction tables (Tables 19a, 19b, and 19d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs. |

**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 | HAD | **Avoid EFV-based regimens if possible.**<br>Favor DTG- or DRV-based regimens. | EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms.<br>There is a theoretical CNS penetration advantage of DTG- or DRV-based regimens. |
| | Medication-assisted treatment for opioid dependence | Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone.<br>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.<br>See the drug-drug interaction tables (Tables 19a, 19b, and 19d) for dosing recommendations. |
| | High cardiac risk | Consider avoiding ABC- and LPV/r -based regimens.<br>If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen.<br>BIC-, DOR-, DTG-, RAL-, or RPV-based regimens may be considered for those with high cardiac risk. | An increased CV risk with ABC has been observed in some studies.<br>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.<br>BIC-, DOR-, DTG-, RAL- or RPV-based regimens have more favorable lipid profiles than other regimens, although evidence on whether this improves CV outcomes is lacking.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. |
| | 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. |
| | Hyperlipidemia | The Following ARV Drugs Have Been Associated with Dyslipidemia:<br>• PI/r or PI/c<br>• EFV<br>• EVG/c<br>BIC, DOR, DTG, RAL, and RPV have fewer lipid effects. | TDF has been associated with lower lipid levels than ABC or TAF.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. |
| | Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care | Consider using regimens with a boosted PI or DTG.<br>BIC also has a high barrier to resistance, but there is currently no data on its efficacy in this population. | These regimens have a high genetic barrier to resistance.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. |

**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 | Pregnancy | Until more information is available, **do not initiate a DTG-based regimen** for those who are pregnant and within 12 weeks post-conception, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[67]<br>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 | Until more information is available, **do not initiate a DTG-based regimen in these patients**, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[67]<br>Refer to Table 6b for further guidance before initiating an INSTI. | |
| **Presence of Coinfections** | HBV infection | Use TDF or TAF, with FTC or 3TC, whenever possible.<br>If TDF and TAF Are Contraindicated:<br>• 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 rifamycins | **TAF and BIC are not recommended with any rifamycin-containing regimen.**<br>If Rifampin is Used:<br>• The following are **not recommended:** PI/c or PI/r, BIC, EVG, DOR, RPV, or TAF.<br>• EFV can be used without dose adjustment.<br>• If RAL is used, increase RAL dose to 800 mg BID. Do **not** use once-daily RAL.<br>• Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label). | Rifamycins may significantly reduce TAF and BIC exposures.<br>Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, DOR, and RPV.<br>Rifampin has a less significant effect on EFV concentration than on the concentrations of other NNRTIs, PIs, and INSTIs.<br>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.<br>See the drug-drug interaction tables (Tables 19a, 19b, 19c, 19d and 19e) and TB/HIV Coinfection for information on ARV use with rifamycins. |

[a] TAF and TDF are two approved forms of tenofovir. 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 to Acronyms:** 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; 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; UGT = uridine diphosphate glucuronosyltransferase.

## Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

The following sections provide detailed information regarding the characteristics, clinical trial results, adverse effects profile, and the Panel's recommendations for ARV drugs that are recommended as initial therapy for persons with HIV.

## Dual-Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Combination Therapy

**Table 8a. Characteristics of Dual-Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy-Naive Patients**

| | ABC/3TC | TAF/FTC | TDF/FTC | TDF/3TC |
|---|---|---|---|---|
| **Dosing Frequency** | Once daily | Once daily | Once daily | Once daily |
| **Available Coformulations for ART-Naive Patients** | • ABC/3TC<br>• DTG/ABC/3TC | • TAF 25 mg/FTC<br>• BIC/TAF 25 mg/FTC<br>• DRV/c/TAF 10 mg/FTC<br>• EVG/c/TAF 10 mg/FTC<br>• RPV/TAF 25 mg/FTC | • TDF/FTC<br>• EFV/TDF/FTC<br>• EVG/c/TDF/FTC<br>• RPV/TDF/FTC | • TDF/3TC<br>• DOR/TDF/3TC<br>• EFV 600 mg/TDF/3TC<br>• EFV 400 mg/TDF/3TC |
| **Adverse Effects** | ABC:<br>• HSR to ABC is associated with the presence of HLA-B*5701 allele<br>• Increase in CV events is associated with ABC use in some, but not all, cohort studies | TAF:<br>• Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF)<br>• Decrease in BMD (less than with TDF; similar to ABC) | TDF:<br>• Renal insufficiency, proximal renal tubulopathy<br>• Decrease in BMD<br>• Renal and bone toxicity are exacerbated by pharmacologic boosters | TDF:<br>• Renal insufficiency, proximal renal tubulopathy<br>• Decrease in BMD<br>• Renal and bone toxicity are exacerbated by pharmacologic boosters |
| | | FTC: Nail pigmentation | | 3TC: No significant adverse effects |
| **Other Considerations** | • Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to allergy list<br>• If HIV RNA >100,000 copies/mL, use only with DTG | Also used for HBV treatment. Discontinuation may precipitate flair of HBV.<br>See Appendix B, Table 8 for dose recommendations in patients with renal insufficiency. | | |

**Key to Acronyms:** 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; STR = single-tablet regimen; 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 due to high rates of serious toxicities, including bone marrow suppression from ZDV use. Other toxicities that mainly occur due to mitochondrial toxicity may lead to myopathy, peripheral neuropathy, hepatic steatosis, lactic acidosis, and lipoatrophy. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.[26,27]

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended for use as components of initial therapy. 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. TAF and TDF are two approved forms of tenofovir. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.[28] 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 and TDF/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[10,29,30] (see also the discussion in the DTG section).[31]

- 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 was used in combination with either EFV or ATV/r. In patients with baseline HIV RNA ≥100,00 copies/mL, there was a significantly shorter time to virologic failure with ABC/3TC than with TDF/FTC regardless of whether the third active drug was EFV or ATV/r.[10] In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. Virologic efficacy was similar in the two study arms, including in a subgroup with HIV RNA ≥100,000 copies/mL.[30]
- 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.[29]

### 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 estimated glomerular filtration rate (eGFR) ≥50 mL/min.
  - TAF/FTC was virologically noninferior to TDF/FTC at week 48 (92% vs. 90% of participants achieved plasma HIV RNA <50 copies/mL, respectively),[32] but TAF/FTC was superior to TDF/FTC at week 144 (84.2% vs. 80%), largely driven by a higher rate of treatment discontinuation in the TDF arm.[33]
  - 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.[33] They also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through week 96.[34] 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.[35]

- Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC each administered in combination with boosted DRV in ART-naive subjects:
  - A Phase 2 study of coformulated DRV/c plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% vs. 74%) in treatment-naive patients.[36] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.
  - 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.[37]
- 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 or 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 due to renal or bone adverse events or fractures. However, bone- and renal-related toxicities were more pronounced when TDF was used in combination with RTV or COBI.[28]
- 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 log10 IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[38] In this study, 96% of participants were on a TDF/FTC-containing regimen prior to the switch. Key results of the study showed that:
  - Those who switched to EVG/c/TAF/FTC maintained HIV suppression: 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 had HBV DNA <29 $\log_{10}$ IU/mL.
  - Decreases in markers of proximal tubular proteinuria and biomarkers of bone turnover were seen in those who switched to EVG/c/TAF/FTC.[38]

## *Dual-Nucleoside Reverse Transcriptase Inhibitor Choices* (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.[31,39-41]

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 will have an ABC-related HSR if given this drug.[42,43] HLA-B*5701 testing should be done if the use of ABC is being considered. In a patient who tests positive for HLA-B*5701, ABC should not be given and ABC hypersensitivity should be noted on the 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 MI, particularly in participants with pre-existing cardiac risk factors.[19,44]

- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association [45-51] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[18,52-55]
- 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.[56]
- 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, 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.

### 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 TDF. The clinical significance of this finding is not clear.[32,57,58]

Other Factors and Considerations:

- TAF/FTC is available in FDCs with 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 eGFRs <15 mL/min.[59]
- 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).[58]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[60] 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.[61,62-70] In a 10-day, open-label, randomized monotherapy trial that was not powered to find a difference between the arms, FTC 200 mg once daily demonstrated a viral load reduction of 1.7 $\log_{10}$ from baseline, compared with a reduction of 1.5 $\log_{10}$ from baseline for 3TC 150 mg twice daily.[71] In a meta-analysis of 12 trials, no significant difference in treatment success was found between 3TC and FTC.[72] In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with an NNRTI (EFV or NVP)[73] or with a boosted PI.[74] TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis; however, it is worth noting that the people in this cohort who were taking 3TC generally had higher viral loads, lower CD4 cell counts, and were more likely to be using injection drugs at the start of the study than people who were taking FTC.[73] 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.[74] 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.[75]

Adverse Effects

*Renal Effects:*

- New onset or worsening renal impairment has been associated with TDF use.[76,77] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)[78] and pre-existing renal impairment.[79] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that there is a greater risk of renal dysfunction 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.[77,79-83]
- 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.[28]

*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.[84,85] 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.[86]
- 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 discontinuation due to bone adverse events occur more frequently among patients who take TDF/FTC with PK boosting.[28]

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 (creatinine clearance [CrCl] <60 mL/min),[87] 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 8 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HIV/HBV 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.
- Specific attention should be given to renal and bone safety monitoring when TDF is used, especially with PK boosters. 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**

**Note:** Preliminary data suggest that there may be an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Until more information is available:

- Pregnancy testing should be performed for those of childbearing potential prior to initiation of ART.
- DTG **is not recommended** for ART-naive individuals:
  - Who are pregnant and within 12 weeks post-conception, *or*
  - Who are of childbearing potential and who are planning to become pregnant or who are sexually active and not using effective contraception.

Clinicians should refer to Table 6b for further guidance before initiating an INSTI.

| | BIC | DTG | EVG | RAL |
|---|---|---|---|---|
| **Dosing Frequency** | Once daily | Once Daily:<br>• In ART-naive or INSTI-naive persons<br>Twice Daily:<br>• If used with certain CYP3A4 and UGT1A1 inducers; *or*<br>• In INSTI-experienced persons with certain INSTI DRMs | Once daily; requires boosting with COBI | • 400 mg BID, *or*<br>• 1200 mg (two 600-mg tablets) once daily |
| **STR Available for ART-Naive Patients** | BIC/TAF/FTC | DTG/ABC/3TC | • EVG/c/TAF/FTC<br>• EVG/c/TDF/FTC | No |
| **Available as a Single-Drug Tablet** | No | Yes | No | Yes |
| **Approved for ART-Experienced Patients** | No | Yes, with BID dosing for patients with some INSTI DRMs | No | Yes, for patients with DRM to PI/r or NNRTIs, but no DRM to INSTIs |
| **Virologic Efficacy Against EVG- or RAL-Resistant HIV** | *In vitro* data indicate activity, but no clinical trial data are available | Yes, for some isolates; effective with 50 mg BID dose | No | No |
| **Adverse Effects** | Nausea, diarrhea (GI disturbance greater with EVG/c), headache, insomnia. 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 19d 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 to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DRM = drug resistance mutation; 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 anionic 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. 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. BIC, DTG, and EVG are available as components of STRs—BIC is coformulated with TAF/FTC, DTG is coformulated with ABC/3TC, and EVG is coformulated with a PK enhancer (COBI) and either TAF/FTC or TDF/FTC. The Panel classifies the three unboosted INSTI-based regimens (BIC, DTG, and RAL) as Recommended Initial Regimens for Most People with HIV. 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. In clinical trials of ART-naive patients who received BIC or DTG plus two NRTIs, resistance was not seen at virologic failure. Because of its high barrier to resistance, DTG may be considered for patients who must start ART before resistance test results are available (e.g., during acute HIV infection and in the setting of certain opportunistic infections). EVG-based regimens are now considered Recommended Initial Regimens in Certain Clinical Situations, because they require boosting with COBI, which results in a greater potential for interaction with concomitant medications.

Preliminary data from an observational study in Botswana suggest that there may be an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Until more information is available, **DTG-based regimens are not recommended for use in ART-naive patients who are pregnant and within 12 weeks post-conception**. These regimens also should not be used in those of childbearing potential who are sexually active and not using effective contraception or who are planning to become pregnant.

It is unclear whether DTG is the only INSTI with the potential to cause NTDs, or if other INSTIs also carry this risk (i.e., a class effect). Table 6b provides recommendations on the use of INSTIs in those who are pregnant or of childbearing potential.

## 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 the 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 48, 89% of participants in the BIC arm and 93% of those in the DTG arm achieved HIV RNA <50 copies/mL ($P = 0.12$).[31]
  - The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At week 48, 92.4% of participants in the BIC/TAF/FTC arm and 93% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL ($P = 0.78$).[5]

Adverse Effects:

- BIC is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of all grades with an incidence ≥5% included diarrhea, nausea, and headache.

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.[88]
- 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, it 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 Table 19d for dosing recommendations when using BIC with these products.
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are typically observed within the first 4 weeks (with a median increase of 0.10 mg/dL after 48 weeks). This effect on creatinine secretion is similar to that seen with other medications used in people with HIV, including DTG 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.
- BIC and DTG share a similar chemical structure. It is unclear whether DTG is the only INSTI with the potential to cause NTDs or if other INSTIs also carry this risk.

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)**.
- Because there are no safety data for the use of BIC around the time of conception to guide evidence-based recommendations, a similar approach to the one outlined for DTG should be discussed before considering the use of BIC-containing ART in those of childbearing potential. The use of BIC-containing ART is not recommended during pregnancy.

**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. It is given once daily, with or without food. Preliminary data from Botswana suggest that there may be an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception.[6,7] More detailed discussions of this potential risk and recommendations for the use of this drug 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 five 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).[4,5]
- 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 regimen (either ABC/3TC or TDF/FTC) to 822 participants. At week 96, DTG was noninferior to RAL.[70]

*DTG/ABC/3TC versus EFV/TDF/FTC:*

- The SINGLE trial compared the use of DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At week 48, DTG was superior to EFV, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[31] At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[89]

*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 because of the higher rate of discontinuation in the DRV/r arm.[90] 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.[91]
- 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 achieved HIV RNA viral loads <50 copies/mL compared with 71% in the ATV group ($P = 0.005$). The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.[92]

*DTG plus Two NRTIs versus DTG plus 3TC:*

- Data are emerging that support the use of two-drug therapy with DTG plus 3TC. The results of a large randomized controlled trial that compared DTG plus TDF/FTC with DTG plus 3TC are discussed in the Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used section below.

Adverse Effects:

- DTG is generally well tolerated. The most commonly reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- Case series of neuropsychiatric adverse events (sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.[93,94] 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.[95,96] However, analyses of data from large randomized controlled trials as well as a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and other ARV regimens,[97] 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,[98] 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.

- Preliminary data from an observational surveillance study of birth outcomes among pregnant women on ART in Botswana identified NTDs in four infants born to 596 women (0.67%) who initiated a DTG-based regimen prior to pregnancy, and who were still receiving it at 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%.[6] This study is ongoing, and more data from births among women who were using a DTG-based regimen around the time of conception are expected. See Table 6b for recommendations on prescribing INSTIs as part of initial therapy.

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 (mean increase in serum creatinine was 0.11 mg/dL after 48 weeks).
- 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. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have not been reported in patients receiving DTG as part of a three-drug regimen for initial therapy, 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 **(AI)** as a Recommended Initial Regimen for Most People with HIV.
- A pregnancy test should be performed for those of childbearing potential prior to initiation of DTG **(AIII)**.
- For those of childbearing potential who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG with the individual **(BIII)**.
- Until more information is available, DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception **(AII)**, *or*
  - Who are of childbearing potential and who are planning to become pregnant **(AII)** or who are sexually active and not using effective contraception **(AIII)**.

### 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.[66] RAL was superior to EFV at 4 and 5 years,[69,99] 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.[70]
- 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 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.[11]

*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 cell count.[100]

Adverse Effects:

- 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.[101]
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see the discussion under DTG).[97,102]

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 19d for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.

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.

- Because fewer patients have received RAL plus ABC/3TC in clinical trials or practice and there has not been a randomized trial comparing ABC/3TC plus RAL to TDF/FTC plus RAL, the Panel categorizes RAL plus ABC/3TC as a Recommended Initial Regimen in Certain Clinical Situations **(BII)**.

### *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.[103]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[104]
  - In a randomized, blinded trial performed in women with HIV, EVG/c/TDF/FTC had superior efficacy when compared to ATV/r plus TDF/FTC, 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.[32,33]
  - 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.[33]

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[103,104]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[103]
- 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 inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see Drug-Drug Interactions).[105]
- Administering 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 dosing.

- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.[107] 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.[83]
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.[83]
- EVG/c/TAF/FTC **is not recommended** for patients with pretreatment estimated CrCl <30 mL/min.
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.[103,104] These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.

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; 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**

| | 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<br>• EFV 600 mg/TDF/3TC<br>• EFV 400 mg/TDF/3TC | • RPV/TAF/FTC<br>• 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, somnolence, and insomnia<br>• Skin rash | • Depression, headache<br>• Skin rash<br>• QT 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 to Acronyms:** 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], nevirapine [NVP], and RPV) are currently approved by the 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[108] and the drugs' low barrier for the development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see Drug-Resistance Testing). 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.[109,110] 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 STRs.[9]
  - At 48 weeks, DOR/TDF/3TC was found to be 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. 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.
  - The DOR group had no change in LDL cholesterol and non-HDL cholesterol among participants, whereas both LDL and non-HDL cholesterol 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.[111]

*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.[8]
- At 48 weeks, DOR was found to be noninferior to DRV/r when these drugs were administered with two NRTIs. Eighty-four percent of study participants receiving DOR achieved HIV RNA <50 copies/mL at 48 weeks, compared to 80% of participants receiving DRV/r.
- 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;[112] there was 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[113] and as part of an STR that contains DOR/TDF/FTC 100 mg/300 mg/300 mg[114] 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 19b).
- 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.[115]
- 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 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, but the Panel has less confidence in this regimen than in the other DOR-containing regimens listed above **(CI)**.

**Efavirenz (EFV)**

Efficacy 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. In clinical trials, EFV-based regimens have demonstrated superiority or noninferiority to several comparator regimens in ART-naive patients.
- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[116]
- 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.[117]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[103]
- 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.

Some regimens have demonstrated superiority to EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to EFV at the primary endpoint of viral suppression at week 48.[31]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks,[66] but RAL was superior to EFV at 4 and 5 years,[69,95] 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.[118]

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.[119] While the frequency of overall adverse events was not different between groups, EFV-related adverse events 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. However, long-term experience and clinical efficacy data regarding its use during pregnancy and in patients with TB/HIV coinfection are lacking.

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, various large studies have provided different results. 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).[120] 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.[121] This association, however, was not found in analyses of three large observational cohorts,[122,123] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[124] A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried an increased risk of suicidal ideation or depression compared to NVP.[125]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[126,127] Consider an alternative therapy 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 STR tablet that uses 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 who weigh ≥35 kg.[128,129]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6; therefore, it may potentially interact with other drugs that use the same pathways (see Tables 19b, 20a, and 20b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.[130] A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).[131]
- Screening for depression and suicidality is recommended for people with HIV who are taking a regimen that includes EFV.

The Panel's Recommendations:

- Given the availability of regimens with fewer treatment-limiting adverse events and also with noninferior or superior efficacy, the Panel classifies EFV/TDF/FTC or EFV/TDF/3TC **(BI)** or EFV plus TAF/FTC **(BII)** as Recommended Initial Regimens in Certain Clinical Situations.
- Randomized clinical trial data have demonstrated the efficacy of lower-dose (400 mg) EFV,[119] but this dose has not been studied in a U.S. population, in pregnant women, or in patients with TB/HIV coinfection. The Panel therefore classifies the use of reduced-dose EFV as a Recommended Initial Regimen in Certain Clinical Situations **(CI)**.

**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.[117] 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 was 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 cell counts <200 cells/mm$^3$ than in those with CD4 cell counts ≥200 cells/mm$^3$.
- STaR, a Phase 3b, open-label study, compared the FDC of RPV/TDF/FTC and EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks[132] were similar to the findings reported at 48 weeks.[118]
  - 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 FDC tablet of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence

study. In this study, participants taking the coformulated drug had plasma concentrations of RPV, FTC, and TAF 25 mg that were similar to concentrations seen in participants who received RPV as the single-drug tablet and TAF/FTC when given as part of the FDC of EVG/c/TAF 10 mg/FTC.[68]

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 with severe depressive symptoms should be evaluated to assess whether 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.[133] 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 cell 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**

| | ATV | DRV |
|---|---|---|
| **Dosing Frequency** | Once daily | • Once daily for PI-naive patients<br>• 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<br>• DRV/c/TAF/FTC |
| **Available as a Single-Drug Tablet** | Yes | Yes |
| **Adverse Effects** | • Jaundice<br>• Indirect hyperbilirubinemia<br>• Cholelithiasis<br>• Nephrolithiasis<br>• PR prolongation | • Skin rash<br>• Increase in serum transaminases<br>• Hyperlipidemia<br>• 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 19a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents. | N/A |

**Key to Acronyms:** 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; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

### *Summary*

FDA-approved PIs include ATV, ATV/c, DRV, DRV/c, fosamprenavir (FPV), indinavir (IDV), LPV/r, nelfinavir (NFV), RTV, saquinavir (SQV), and tipranavir (TPV). 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.[134,135] For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy due to 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 3.

PIs 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 together 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.[11]

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.[19-20,33] Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens compared to those receiving other regimens.[22] 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 included 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,[44] and superior at week 192.[136] 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 excess failure observed in the DRV/r group was primarily related to a higher rate of virologic failure among those with a viral loads >100,000 copies/mL and secondarily due to more drug discontinuations in the DRV/r group.[14]
- ACTG A5257, a large randomized open-label trial, compared ATV/r with 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.[11]
- 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 achieving HIV RNA levels <50 copies/mL compared with 84% of participants who received DRV/r.

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.[11] 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 ($P \leq 0.02$).[137]
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.[23]

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 who did or did not have 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)**

A combination of DRV 800 mg with COBI 150 mg is bioequivalent to DRV 800 mg with RTV 100 mg in healthy volunteers, based on the maximum concentration and area under the concentration time curve for DRV.[138] 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.[139]

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%, 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.[37]
- 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.[140]

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 Situations.
- 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.[141]

*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.[116] 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.[142]

*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.[104] 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 discontinued therapy because of adverse events, compared to five women in the INSTI arm.
- 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, DTG was found to have a rate of virologic suppression (<50 copies/mL) that was noninferior to the rate seen in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.[92]

*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.[11]

*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.[143] 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.[144]

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.[145]
- Nephrolithiasis,[146-148] nephrotoxicity,[21] and cholelithiasis[149] 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 19a 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.[18-20,23] Another study of an observational cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens compared with participants receiving other regimens.[22] 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.[10]
- 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

All currently recommended ARV regimens consist of two NRTIs plus a third active drug. This strategy, however, may not be possible or optimal in all patients. In some situations, it may be necessary 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. To address these concerns, several clinical studies have evaluated strategies using initial regimens that avoid the use of two NRTIs or the NRTI drug class altogether. 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 plus Lamivudine (DTG plus 3TC)

- In the GEMINI-1 and -2 trials, a total of 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At week 48, DTG plus 3TC was noninferior to DTG plus TDF/FTC with respect to the proportion of participants with viral loads <50 copies/mL (91% and 93%, respectively).[12] Virologic nonresponse was uncommon, occurring in 3% 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. Longer term follow up is ongoing.
- The PADDLE trial was a small, single-arm study of DTG plus 3TC in 20 ART-naive adults with baseline HIV RNA <100,000 copies/mL. At 48 weeks, 18 out of 20 subjects (90%) achieved HIV RNA <50 copies/mL.[150] Fifteen of these 18 participants completed 96 weeks of treatment and maintained HIV RNA <50 copies/mL.[151]
- The ACTG A5353 trial evaluated this same regimen in a single-arm trial that included ART-naive participants with a baseline HIV RNA of up to 500,000 copies/mL and no genotypic NRTI, INSTI, or PI resistance. The trial enrolled 120 participants; 37 participants (30.8%) had a baseline HIV RNA >100,000

copies/mL. At week 24, 90% of participants had HIV RNA <50 copies/mL; there were similar response rates in participants with baseline HIV RNA >100,000 copies/mL and ≤100,000 copies/mL (89% and 90%, respectively). Three participants experienced virologic failure, all of whom had suboptimal adherence; one participant developed an NRTI resistance mutation (M184V) and an INSTI resistance mutation (R263K).[152]

The Panel's Recommendation:

- On the basis of these study results, the Panel recommends the use of DTG plus 3TC in ART-naive adults with baseline HIV RNA <500,0000 copies/mL in instances where ABC, TAF, or TDF cannot be used or are not optimal **(BI)**.
- Preliminary data from an observational study in Botswana suggest that there may be an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Clinicians should refer to Table 6b prior to initiation of DTG in those who are pregnant or those who are of childbearing potential.

**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.[25] The dual- and triple-therapy groups had similar rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL (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 cell counts <200 cells/mm$^3$, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.[24] 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.[153,154]

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 cell counts >200 cells/mm$^3$, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

## *A Nucleoside-Limiting Regimen that is Efficacious but has Disadvantages*

**Lopinavir/Ritonavir plus Lamivudine (LPV/r plus 3TC)**

- In the GARDEL study, 426 ART-naive patients were randomized to receive twice-daily LPV/r plus either

open-label 3TC (twice daily) or two NRTIs selected by the study investigators. At 48 weeks, a similar proportion of patients in each arm had HIV RNA <50 copies/mL (88.3% vs. 83.7%), meeting the study's noninferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus two NRTI regimen.[155]

- This regimen is used infrequently due to the requirement of twice-daily dosing, the relatively high pill burden (a total of 5–6 tablets per day), and the adverse effect profile of LPV/r. In view of these substantial limitations, the Panel recommends that LPV/r plus 3TC be considered for use only in patients who cannot take ABC, TAF, or TDF and in whom the other alternatives listed above cannot be used **(CI)**.

**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 | ABC/3TC | • Coformulated with DTG<br>• 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.<br>• 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.<br>• 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<br>• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection<br>• Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC<br>• Approved for patients with eGFR ≥30 mL/min | • TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. |
| | TDF/3TC | • Coformulated with DOR and EFV<br>• Available as the following generic formulations:<br>  • TDF<br>  • 3TC<br>  • TDF/3TC<br>  • EFV/TDF/3TC<br>• Long-term clinical experience<br>• Active against HBV | • Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters.<br>• Osteomalacia has been reported as a consequence of proximal tubulopathy.<br>• 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<br>• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection<br>• Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV<br>• 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.<br>• Osteomalacia has been reported as a consequence of proximal tubulopathy.<br>• 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) |
|---|---|---|---|
| INSTI | BIC | • Coformulated with TAF/FTC<br>• In trials in ART-naive participants, BIC resistance was not detected<br>• No food requirement | • Compared to other INSTIs, BIC has the shortest post-marketing experience.<br>• 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 19d.<br>• Inhibits tubular secretion of creatinine without affecting glomerular function.<br>• CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug interactions. |
| | DTG | • Higher barrier to resistance than EVG or RAL<br>• Coformulated with ABC and 3TC<br>• No food requirement<br>• No CYP3A4 interactions<br>• Favorable lipid profile | • Preliminary data suggests that DTG use before pregnancy and through conception may be associated with an increased risk of NTDs in the infant. See text and Table 6b for recommendations.<br>• 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 19d.<br>• Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function.<br>• UGT1A1 substrate; potential for drug interactions (see Table 19d).<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). |
| | EVG/c | • Coformulated with TDF/FTC or TAF/FTC<br>• Compared with ATV/r, causes smaller increases in total and LDL cholesterol | • 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.<br>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.<br>• 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 19d.<br>• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function.<br>• Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens.<br>• Food requirement.<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). |

**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 | RAL | • Compared to other INSTIs, has longest post-marketing experience<br>• No food requirement<br>• No CYP3A4 interactions<br>• Favorable lipid profile | • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens.<br>• Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported.<br>• Rare cases of severe HSRs (including SJS and TEN) have been reported.<br>• Higher pill burden than other INSTI-based regimens.<br>• No STR formulation.<br>• 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 19d.<br>• UGT1A1 substrate; potential for drug interactions (see Table 19d).<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). |
| NNRTI | DOR | • Coformulated with TDF/3TC<br>• Compared to EFV, CNS side effects are less frequent<br>• No food requirement<br>• Favorable lipid profile | • Shorter-term clinical experience than with EFV and RPV.<br>• Potential for CYP450 drug interactions (see Tables 19b, 20a and 20b).<br>• Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs. |
| | EFV | • EFV 600 mg is coformulated with TDF/FTC and TDF/3TC<br>• EFV 400 mg is coformulated with TDF/3TC<br>• 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 | • Short-and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV.<br>• Teratogenic in nonhuman primates, although no rate increase has been seen in humans.<br>• Dyslipidemia<br>• Rash<br>• 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.<br>• Transmitted resistance is more common than with PIs and INSTIs.<br>• Greater risk of resistance at the time of treatment failure than with PIs.<br>• Potential for CYP450 drug interactions (see Tables 19b and 20a).<br>• Should be taken on an empty stomach (food increases drug absorption and CNS toxicities). |

**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 | RPV | • Coformulated with TDF/FTC and TAF/FTC<br>• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs<br>• Compared with EFV:<br>  • Fewer CNS adverse effects<br>  • Fewer lipid effects<br>  • Fewer rashes | • **Not recommended** in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 cell counts <200 cells/mm$^3$ because of higher rate of virologic failure in these patients.<br>• Depression and suicidality<br>• 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.<br>• Rash<br>• Transmitted resistance is more common than with PIs and INSTIs.<br>• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.<br>• Potential for CYP450 drug interactions (see Tables 19b and 20a).<br>• Meal requirement (>390 kcal)<br>• Requires acid for adequate absorption.<br>  • **Contraindicated** with PPIs.<br>  • Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information). |
| PIs | ATV/c or ATV/r | • Higher barrier to resistance than NNRTIs, EVG, and RAL.<br>• PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs<br>• ATV/c and ATV/r have similar virologic activity and toxicity profiles<br>• 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.<br>• Individual ATV and RTV components available as generics | • Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice.<br>• Food requirement<br>• Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs).<br>• Nephrolithiasis, cholelithiasis, nephrotoxicity<br>• GI adverse effects<br>• CYP3A4 inhibitors and substrates; potential for drug interactions (see Table 19a). |
| | ATV/c (Specific considerations) | • Coformulated tablet | • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function.<br>• Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min.<br>• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. |
| | DRV/c or DRV/r | • Higher barrier to resistance than NNRTIs, EVG, and RAL.<br>• PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs | • Skin rash<br>• Food requirement<br>• GI adverse effects<br>• CYP3A4 inhibitors and substrates; potential for drug interactions (see Table 19a).<br>• Increased CV risk reported in one observational cohort study. |

**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 | 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.<br>• Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min.<br>• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. |
| | LPV/r | • Only RTV-coformulated PI<br>• No food requirement | • Requires RTV 200 mg per day.<br>• Possible higher risk of MI associated with cumulative use of LPV/r.<br>• PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or in patients receiving other drugs with similar effects.<br>• Possible nephrotoxicity<br>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 19a). |

**Key to Acronyms:** 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; eGFR = estimated glomerular filtration rate; EFV = efavirenz; 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 = lopinavir; 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 3)

| ARV Components or Regimens | Reasons for Not Recommending as Initial Therapy |
|---|---|
| **NRTIs** | |
| **ABC/3TC/ZDV (Coformulated)**<br>As triple-NRTI combination regimen | • Inferior virologic efficacy |
| **ABC/3TC/ZDV plus TDF**<br>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<br>• Limited clinical trial experience in ART-naive patients<br>• ddI toxicities, such as pancreatitis and peripheral neuropathy |
| **ddI plus TDF** | • High rate of early virologic failure<br>• Rapid selection of resistance mutations<br>• Potential for immunologic nonresponse/CD4 cell decline<br>• Increased ddI drug exposure and toxicities |

**Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy** (page 2 of 3)

| ARV Components or Regimens | Reasons for Not Recommending as Initial Therapy |
|---|---|
| **NRTIs**, continued | |
| **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<br>• 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)<br>• 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)**<br>or<br>**FPV/r** | • Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV<br>• Less clinical trial data for FPV/r than for other RTV-boosted PIs |
| **IDV (Unboosted)** | • Inconvenient dosing (3 times daily with meal restrictions)<br>• Fluid requirement<br>• IDV toxicities, such as nephrolithiasis and crystalluria |
| **IDV/r** | • Fluid requirement<br>• IDV toxicities, such as nephrolithiasis and crystalluria |
| **LPV/r** | • Higher pill burden than other PI-based regimens<br>• Higher RTV dose than other PI-based regimens<br>• GI intolerance |
| **NFV** | • Inferior virologic efficacy<br>• Diarrhea |
| **RTV as sole PI** | • High pill burden<br>• GI intolerance<br>• Metabolic toxicity |
| **SQV (Unboosted)** | • Inadequate bioavailability<br>• Inferior virologic efficacy |
| **SQV/r** | • High pill burden<br>• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG |
| **TPV/r** | • Inferior virologic efficacy<br>• Higher rate of adverse events than other RTV-boosted PIs<br>• Higher dose of RTV required for boosting than other RTV-boosted PIs |
| **Entry Inhibitors** | |
| **T-20**<br>Fusion Inhibitor | • Only studied in patients with virologic failure<br>• Twice-daily subcutaneous injections<br>• High rate of injection site reactions |
| **IBA**<br>CD4 Post-Attachment Inhibitor | • Only studied in a very small number of patients with virologic failure<br>• Requires IV therapy<br>• High cost |

**Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy** (page 3 of 3)

| ARV Components or Regimens | Reasons for Not Recommending as Initial Therapy |
|---|---|
| **Entry Inhibitors**, continued | |
| **MVC**<br>CCR5 Antagonist | • Requires testing for CCR5 tropism before initiation of therapy<br>• No virologic benefit when compared with other recommended regimens<br>• Requires twice-daily dosing |

**Key to Acronyms:** 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 19a and 19d).

### 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)**.[21]

### 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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