Management of the Treatment-Experienced Patient

Virologic Failure (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- Assessing and managing a patient who is experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
- Evaluation of virologic failure should include an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance test results.
- Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen **(AI)** or within 4 weeks of treatment discontinuation **(AII)**. Even if more than 4 weeks have elapsed since ARVs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII)**.
- The goal of treatment for ART-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays) **(AI)**.
- A new regimen should include at least two, and preferably three, fully active agents **(AI)**. A fully active agent is one that is expected to have uncompromised activity on the basis of the patient's ART history and his or her current and past drug-resistance test results. A fully active agent may also have a novel mechanism of action.
- In general, adding a single ARV agent to a virologically failing regimen **is not recommended**, because this may risk the development of resistance to all drugs in the regimen **(BII)**.
- For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.
- It is crucial to provide continuous adherence support to all patients before and after regimen changes due to virologic failure.
- Preliminary data suggest that there is an increased risk of neural tube defects in infants born to individuals who were receiving dolutegravir (DTG) at the time of conception. In patients with virologic failure who are of childbearing potential, pregnancy testing should be performed before starting DTG **(AIII)**.
- For patients who are pregnant and within 12 weeks post-conception, or those who are of childbearing potential and who are not using effective contraception or who are contemplating pregnancy, the following factors should be considered:
  - If an alternative active ARV option to DTG exists, DTG should not be prescribed **(AII)**.
  - If no alternatives exist, providers and individuals of childbearing potential should discuss the possible association between neural tube defects and DTG use during conception, and the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after careful consideration of these risks.
- When it is not possible to construct a viable suppressive regimen for a patient with multidrug-resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.
- When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and an increase in the risk of clinical progression. Therefore, this strategy **is not recommended** in the setting of virologic failure **(AI)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral (ARV) regimens that are currently recommended for initial therapy in patients with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels that are below the lower limits of detection (LLOD) of currently used assays (see What to Start). Patients on antiretroviral therapy (ART) who do not achieve this treatment goal or who experience virologic rebound can develop resistance mutations to one or more components of their regimen. Adherence to ART regimens can be challenging for some patients, and poor adherence can result in detectable viral loads. Depending on their treatment histories, some of these patients may have minimal or no drug resistance; others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients on ART and discusses strategies to manage ART in these individuals.

Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to ART:

Virologic Suppression: A confirmed HIV RNA level below the LLOD of available assays.

Virologic Failure: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

Incomplete Virologic Response: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen. A patient's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels.

Virologic Rebound: Confirmed HIV RNA level ≥200 copies/mL after virologic suppression.

Virologic Blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Low-Level Viremia: Confirmed detectable HIV RNA level <200 copies/mL.

Antiretroviral Therapy Treatment Goals and Presence of Viremia While on Antiretroviral Therapy

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to below the LLOD of current assays.[1]

Virologic blips are not usually associated with subsequent virologic failure.[2] In contrast, there is controversy regarding the clinical implications of persistently low HIV RNA levels that are between the LLOD and <200 copies/mL in patients on ART. Viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than the PCR-based viral load platforms used in the past.[3-5] Findings from a large retrospective analysis showed that, as a threshold for virologic failure, HIV RNA levels of <200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound as HIV RNA levels of >200 copies/mL.[6] Two other retrospective studies also support the supposition that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL.[7,8] However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound[9,10] and can be associated with the evolution of drug resistance.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common when HIV RNA levels are >500 copies/mL.[13] Therefore, persistent plasma HIV RNA levels ≥200 copies/mL are considered virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.[14,15] The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.[16] Virologic failure may be associated with various patient/adherence-, HIV-, and regimen-related factors, as listed below.

Patient/Adherence-Related Factors (see Adherence to the Continuum of Care)

- Comorbidities that may affect adherence (e.g., active substance abuse, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARVs (i.e., these factors may affect the ability to access or continue therapy)
- Drug adverse effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance test results
- Prior treatment failure
- Innate resistance to ARVs due to viral tropism or the presence of HIV-2 infection/coinfection
- Higher pretreatment HIV RNA level (some regimens may be less effective at higher levels)

Antiretroviral Regimen-Related Factors

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or possible penetration into reservoirs)
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual nucleoside reverse transcriptase inhibitor (NRTI) therapy, or the sequential introduction of drugs)
- Food requirements
- Adverse drug-drug interactions with concomitant medications
- Prescription errors

Managing Patients with Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above factors could have been the cause(s) of failure is indicated. Often the causes of virologic failure can be identified, but in some cases they are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ. Potential causes of virologic failure should

be explored in depth. Once virologic failure is confirmed, steps should be undertaken to improve virologic outcomes. Those approaches are outlined below.

Key Factors to Consider When Designing a New Antiretroviral Regimen

- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose predicted activity is based on the patient's ART history, current and previous resistance test results, or a new mechanistic action **(AI)**.[9,17-26]
- Despite the presence of some drug resistance mutations, some ARV drugs in the regimen may still have partial activity against the patients' HIV and may be retained as part of a salvage regimen. These drugs may include NRTIs or protease inhibitors (PIs).[27] Other agents will likely have to be discontinued, as their continued use may lead to further accumulation of resistance mutations and jeopardize treatment options with newer drugs from the same drug class. These drugs may include enfuvirtide (T-20); non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz (EFV), nevirapine (NVP), and rilpivirine (RPV); and the first-generation integrase strands transfer inhibitors (INSTIs) raltegravir (RAL) and elvitegravir (EVG).[28-30]
- Using a "new" drug that a patient has never used previously does not ensure that the drug will be fully active; there is a potential for cross-resistance among drugs from the same class.
- Archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question.
- When constructing a salvage regimen, it is more important to consider drug potency and viral susceptibility based on cumulative genotype data than the number of component drugs.
- Resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient's plasma HIV RNA level is >1,000 copies/mL **(AI)**, and possibly even if it is between 500 to 1,000 copies/mL **(BII)** (see Drug-Resistance Testing). In some patients, resistance testing should still be considered even after treatment interruptions of >4 weeks, though clinicians should recognize that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels **(CIII)**. Drug resistance is cumulative; thus, clinicians should evaluate the extent of drug resistance, taking into account prior ART history and, importantly, prior genotypic or phenotypic resistance test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs, whereas INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in patients who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for patients who experience failure on a fusion inhibitor **(AII)** and viral tropism tests for patients who experience failure on a CCR5 antagonist **(BIII)** are also available (see Drug-Resistance Testing).
- Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia **is not recommended**, as it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count, and it increases the risk of clinical progression **(AI)**[27,31] (see Discontinuation or Interruption of Antiretroviral Therapy).
- When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see Hepatitis B (HBV)/HIV Coinfection).

Antiretroviral Strategies

- In general, patients who receive at least three active drugs experience better and more sustained virologic

response than those receiving fewer active drugs. These three drugs should be selected based on the patient's ART history and a review of their drug-resistance test results, both past and present.[18,19,21,22,32-34]

- Active drugs are ARVs that, based on current and previous resistance test results and ART history, are expected to have antiviral activity equivalent to the activity seen when there is no resistance to the specific drugs. ARVs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance.
- Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine [ETR], darunavir [DRV], and dolutegravir [DTG]).
- An active drug may also be one with a mechanism of action that is different from the mechanisms of the ARV drugs that were previously used in that individual (e.g., the fusion inhibitor enfuvirtide, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus, and some investigational ARV drugs).
- An increasing number of studies in ART-naive and ART-experienced patients have shown that an active, pharmacokinetically enhanced PI plus one other active drug or several partially active drugs will effectively reduce viral load in most patients.[35-38]
- In the presence of certain resistance mutations, some ARVs, such as DTG, darunavir/ritonavir (DRV/r), and lopinavir/ritonavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus.[39,40]

Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous group of individuals with different ART exposure histories, extents of drug resistance, durations of virologic failure, and levels of plasma viremia. Management strategies should be individualized. The first steps for all patients with detectable viral loads are to confirm the level of HIV viremia and assess and address adherence and potential drug-drug interactions (including interactions with over-the-counter products and supplements) and drug-food interactions. Some general approaches based on level of viremia are addressed below.

- **HIV RNA Above the LLOD and <200 copies/mL:** Patients who have these HIV RNA levels (i.e., blips) do not typically require a change in treatment **(AII)**.[4] Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future **(AIII)**.
- **HIV RNA Levels ≥200 and <1,000 copies/mL:** In contrast to patients with detectable HIV RNA levels that are persistently <200 copies/mL, those with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[7,8] Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered virologic failure, and resistance testing should be attempted, particularly in patients with HIV RNA levels >500 copies/mL. Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL (as outlined below). When resistance testing cannot be performed because of low HIV RNA levels, the decision of whether to empirically change ARVs should be made on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress viremia can be constructed.
- **HIV RNA ≥1,000 copies/mL and No Drug Resistance Mutations Identified Using Current or Previous Genotypic Resistance Test Results:** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment to determine the level of adherence, identify and address the underlying cause(s) for incomplete adherence and, if possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency; see Adherence to the Continuum of Care). Approaches include:

- Assessing the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence.
- Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI; see Adverse Effects of Antiretroviral Agents).
- Reviewing food requirements for each medication and assessing whether the patient adheres to the requirements.
- Assessing whether there is a recent history of gastrointestinal symptoms (e.g., vomiting or diarrhea) that may result in short-term malabsorption.
- Reviewing concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions and Tables 19a–20b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
- Considering therapeutic drug monitoring if PK drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected.
- Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for >4 weeks before testing?).
  - If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen.
  - If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective but more tolerable regimen.
  - Repeat viral load testing 2 to 4 weeks after treatment is resumed or started; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged **(CIII)**.

- **HIV RNA >1,000 copies/mL and Drug Resistance Identified:** If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible in order to avoid progressive accumulation of resistance mutations.[41] In addition, several studies have shown that virologic responses to new and active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 cell counts at the time of regimen changes; thus, the change is best done before viremia worsens or CD4 count declines.[9,42] The availability of newer ARVs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most of these patients. The options in this setting depend on the extent of drug resistance and are addressed in the clinical scenarios outlined below.

Managing Virologic Failure in Different Clinical Scenarios

See Table 11 for a summary of these recommendations.

Virologic Failure with First Antiretroviral Regimen

- **NNRTI plus NRTI Regimen Failure:** These patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC). Additional NRTI mutations may also be present. Below are some switch options.
  - **Boosted PI plus Two NRTIs:** Three large randomized controlled trials (primarily conducted in resource-limited settings where NNRTI-based regimens have been used as first-line therapy) have explored different second-line regimen options. The studies found that regimens containing LPV/r plus two NRTIs were as effective as regimens containing LPV/r plus RAL.[37,38,43] Even though

LPV/r was the PI used in these studies, it is likely that other PK-boosted PIs (DRV/r or atazanavir/ritonavir [ATV/r]) would have similar activities and may be tolerated better, although this has not been demonstrated in large clinical trials. The EARNEST study randomized participants to receive LPV/r plus two or three investigator-selected NRTIs, LPV/r plus RAL, or LPV alone. Participants did not undergo resistance testing before randomization.[38] Lower rates of virologic suppression were seen with LPV/r monotherapy, confirming that ritonavir-boosted PI (PI/r) monotherapy **cannot be recommended (AI)**.[38,44] The virologic responses were similar in the LPV/r plus NRTIs arm and the LPV/r plus RAL arm. A post-hoc analysis showed that viral suppression was achieved in over 80% of the participants who received either no active NRTIs or one active NRTI in their new regimens.[45] It should be noted that most of the participants received thymidine analogs (stavudine or zidovudine—NRTIs that are no longer used in first-line regimens in the United States) plus 3TC. The authors of this trial suggest that, as a public health approach, resistance testing after first-line failure may not be necessary in resource-limited countries. However, in settings where genotype resistance tests are available, the Panel recommends using a PK-boosted PI plus two NRTIs (at least one of which is active) in a regimen **(AIII)**.

- **DTG plus One or Two Active NRTIs:** In the DAWNING trial, patients who experienced virologic failure while on a first-line, NNRTI-based regimen were randomized to receive either LPV/r or DTG; each of these drugs was given with two NRTIs, one of which had to be fully active based on real-time resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm.[46] Thus, DTG plus two NRTIs (at least one of which is active) can be an option after failure of a first-line, NNRTI-based therapy **(AI)**. Bictegravir (BIC) may have activity that is similar to that of DTG; however, there are currently no data to support its use. There are limited to no data available on the efficacy of EVG or RAL to recommend the use of these INSTIs in the setting of first line NNRTI-based therapy failure.
- **Boosted PI plus an INSTI:** As noted earlier, a regimen consisting of LPV/r plus RAL was found to be as effective as LPV/r plus two NRTIs.[37,38,43] Thus, LPV/r plus RAL can also be a treatment option for those who experienced virologic failure on an NNRTI-based regimen **(AI)**. Although data are limited, DTG combined with a PK-boosted PI may also be an option in this setting **(AIII)**. There are no data on the efficacy of BIC or EVG with boosted PI in the setting of first line NNRTI-based therapy failure.

Preliminary data from Botswana suggested that there is an increased risk of neural tube defects (NTDs) in infants born to individuals who were receiving DTG at the time of conception.[47,48] Pregnancy testing should therefore be performed for those of childbearing potential prior to initiation of DTG. DTG should not be prescribed for patients who are pregnant and within 12 weeks post-conception. It is also not recommended for those of childbearing potential who desire pregnancy or who are sexually active and not using effective contraception. Though BIC is not specifically considered in this section, clinicians should be aware of the structural similarity of BIC and DTG. Since there are no safety data on the use of BIC around the time of conception to guide evidence-based recommendations, an approach similar to that outlined for DTG may be implemented before considering the use of BIC-containing ART in those of childbearing potential.

- **PK-Boosted PI plus NRTI Regimen Failure:** In this scenario, most patients will have either no resistance or resistance that is limited to 3TC and FTC.[49,50] Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. Below are some management options.
  - **Maintain on Same Regimen:** A systematic review of multiple randomized trials that investigated the failures of first-line, PI/r-based regimens showed that maintaining the same regimen while making efforts to enhance adherence is as effective as changing to new regimens with or without drugs from new classes **(AII)**.[51] If the regimen is well tolerated and there are no concerns regarding drug-drug or

drug-food interactions or drug resistance, then the regimen can be continued with adherence support and viral monitoring.

- **Switch to Another Regimen:** If poor tolerability, drug interactions, or drug resistance may be contributing to virologic failure, then the regimen can be modified to:
  - A different boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
  - A different boosted PI plus an INSTI **(BIII)**; *or*
  - An INSTI plus two NRTIs (at least one of which is active) **(AIII)**. As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is the recommended INSTI **(AIII)**. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. There are limited to no data on the efficacy of BIC or EVG in this setting.

- **INSTI plus NRTI Regimen Failure:** Virologic failure in patients on a regimen that consists of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC/FTC and possibly the INSTI.[52] Viruses with EVG or RAL resistance often remain susceptible to DTG.[42] In contrast, in clinical trials, persons who experienced virologic failure while receiving BIC or DTG plus two NRTIs as first-line therapy were unlikely to develop phenotypic resistance to BIC or DTG.[52-54] There are no clinical trial data to guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on resistance test results and the potential potency of the next regimen. Below are some treatment options, based on resistance pattern considerations.
  - **Virologic Failure without Any Resistance Mutations:** The patient should be managed as outlined above in the section on virologic failure without resistance.
  - **Virologic Failure without INSTI Resistance:** The regimen can be modified to:
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - A boosted PI plus an INSTI **(AIII)**; *or*
    - DTG plus two NRTIs (at least one of which is active) **(AIII)**.
  - **Virologic Failure with Resistance to RAL and EVG but Susceptibility to DTG:** The regimen can be modified to:
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus a PK-boosted PI **(AIII)**.

  There are currently no data on the efficacy of BIC in patients who experience virologic failure while on an EVG- or RAL-based regimen; therefore, this drug cannot be recommended in this setting.

Second-Line Regimen Failure and Beyond

Drug Resistance with Fully Active Antiretroviral Therapy Options

Using a patient's treatment history and drug-resistance data, a clinician can decide whether to include a fully active PK-boosted PI in future regimens. For example, those who have no documented PI resistance and have previously never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. In this setting, viral suppression should be achievable using a PK-boosted PI combined with either two NRTIs or an INSTI—provided the virus is susceptible to these drugs. If a fully active, PK-boosted PI is not an option, the new regimen should include at least two, and preferably three, fully active agents. Drugs should be selected based on the likelihood that they will be active, as determined by the patient's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug Resistance without Fully Active Antiretroviral Therapy Options

Use of currently available ARVs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug resistance.[55,56] Despite this progress, there remain patients who have experienced toxicities and/or developed resistance to all or most currently available drugs. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens. Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T-20, DTG, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, as there is little evidence that keeping them on the regimen helps delay disease progression **(BII)**. Moreover, continuing these drugs (in particular INSTIs) may allow for selection of additional resistance mutations and development of within-class cross resistance that may limit future treatment options. It should be noted that even partial virologic suppression of HIV RNA to >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit.[55,57] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 cell count increases, reduces the risk of disease progression.[58] Other cohort studies suggest continued immunologic and clinical benefits with even modest reductions in HIV RNA levels.[59,60] However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single fully active ARV to the regimen **is not recommended** because of the risk of rapid development of resistance **(BII)**.

Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. When DTG is the only treatment option, or one of few treatment options, providers should counsel individuals who are pregnant or of childbearing potential about the possible association between NTDs and DTG use during conception. Providers should also discuss the risks 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 ART. The decision of whether to initiate or continue DTG should be made after careful consideration of all these risks.

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for the recently approved CD4 post-attachment inhibitor ibalizumab (IBA).[61] A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV and who were experiencing virologic failure on an ARV regimen. Subjects received intravenous infusions of IBA every 2 weeks in addition to an optimized background regimen that included at least one additional agent to which the subject's virus was susceptible. At week 24, 43% of participants achieved HIV RNA <50 copies/mL, and 50% of participants achieved HIV RNA <200 copies/mL.[62] Of the 27 participants who continued on to the 48-week follow-up study, 59% and 63% had HIV RNA <50 copies/mL and <200 copies/mL, respectively. All 15 patients who had HIV RNA <50 copies/mL at week 24 maintained viral suppression up to week 48.[63]

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in Food and Drug Administration regulations. Information about agents that are in late-stage clinical studies (e.g., fostemsavir, PRO-140), can be found in the drug fact sheets available on AIDS*info*'s website.

Previously Treated Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Resistance Test Results)

Every effort should be made to obtain the patient's ARV history and prior drug-resistance test results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be active based on the patient's treatment history. If there is no available

ARV history, a clinician may consider using agents with a high barrier to resistance, such as twice-daily DTG and/or boosted DRV, as part of the regimen. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. HIV RNA and resistance testing should be obtained approximately 2 to 4 weeks after re-initiation of therapy, and patients should be closely monitored for virologic responses. Lastly, clinicians should be aware of the structural similarity between BIC and DTG. Since there are no safety data for the use of BIC around the time of conception to guide evidence-based recommendations, an approach similar to that outlined for DTG may be implemented before considering BIC-containing ART in those of childbearing potential.

Table 11. Antiretroviral Options for Patients with Virologic Failure

Designing a new regimen for patients with treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. For more detailed descriptions, please refer to the text above and/or consult an expert in drug resistance to assist in the design of a new regimen. It is also crucial to provide continuous adherence support to all patients before and after regimen changes.

Preliminary data from Botswana suggested that there is an increased risk of NTDs in infants born to individuals who were receiving DTG at the time of conception.[47,48] Pregnancy testing should therefore be performed for those of childbearing potential prior to initiation of DTG. If there is an alternative option, DTG should not be prescribed for those who are pregnant and within 12 weeks post-conception or those who are of childbearing potential and who are planning to become pregnant or who are not using effective contraception. When DTG is the only treatment option, or one of few treatment options, providers should counsel individuals who are pregnant or of childbearing potential about the possible association between NTDs and DTG use during conception. The decision of whether to initiate or continue DTG should be made after careful consideration of this risk and the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure	NNRTI plus 2 NRTIs	Most likely resistant to NNRTI +/- 3TC/FTC (i.e., NNRTI mutations +/- M184V/I).[c] Additional NRTI mutations may also be present.	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**; *or* • DTG[d] plus 2 NRTIs (at least 1 active) **(AI)**; *or* • Boosted PI plus INSTI **(AIII)**	Resuppression
	Boosted PI plus 2 NRTIs	Most likely no resistance, or resistance only to 3TC/FTC (i.e., M184V/I, without resistance to other NRTIs)[c]	• Continue same regimen **(AII)**; *or* • Another boosted PI plus 2 NRTIs (at least 1 active) **(AII)**; *or* • INSTI plus 2 NRTIs (at least 1 active; if only 1 of the NRTIs is fully active, or, if adherence is a concern, DTG[d] is preferred over the other INSTIs) **(AIII)**; *or* • Another boosted PI plus INSTI **(BIII)**	Resuppression
	INSTI plus 2 NRTIs	No INSTI resistance (can have 3TC/FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs)[c]	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**; *or* • DTG[d] plus 2 NRTIs (at least 1 active) **(AIII)**; *or* • Boosted PI plus INSTI **(BIII)**	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure, continued	INSTI plus 2 NRTIs	EVG or RAL +/- 3TC/FTC resistance Resistance to first-line BIC or DTG is rare	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**, *or* • DTG[d,e] twice daily (if patient is sensitive to DTG) plus 2 active NRTIs **(AIII)**; *or* • DTG[d,e] twice daily (if patient is sensitive to DTG) plus a boosted PI **(AIII)** • BIC has not been studied in this setting and **cannot be recommended.**	Resuppression
Second Regimen Failure and Beyond	Drug resistance with active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen	• At least 2, and preferably 3, fully active agents **(AI)** • Partially active drugs may be used when no other options are available • Consider using an ARV with a different mechanism of action	Resuppression
	Multiple or extensive drug resistance with few treatment options	Use past and current genotypic and phenotypic resistance testing to guide therapy Consider viral tropism assay if use of MVC is considered Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance test results • Consider using an ARV with a different mechanism of action • Consider enrollment into clinical trials or expanded access programs for investigational agents, if available • Discontinuation of ARVs **is not recommended.**	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 cell count as high as possible
Previously on Treatment, Suspected Drug Resistance, Limited or Incomplete ART and Resistance History	Unknown	Obtain medical records if possible Resistance testing may be helpful in identifying drug resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	• Consider restarting the old regimen, and obtain viral load and resistance testing 2–4 weeks after reintroduction of therapy • If there is no available ARV history, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG[d,e] and/or boosted DRV)	Resuppression

[a] There are insufficient data to provide a recommendation for the continuation of 3TC/FTC in the presence of M184V/I.

[b] When switching an ARV regimen in a patient with HIV/HBV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[c] If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

[d] Preliminary data from Botswana suggested that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[47,48] Pregnancy testing should therefore be performed for those of childbearing potential prior to initiation of DTG. Please refer to the discussion at the beginning of this table for further recommendations.

[e] Response to DTG depends on the type and number of INSTI mutations.

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of "compartmentalized" virologic failure. These patients present with new, usually subacute, neurological symptoms associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.[64-66] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.[67] Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, there is evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen according to principles outlined above for plasma HIV RNA resistance **(CIII)**. In these patients, it may also be useful to consider CNS PKs in drug selection to assure adequate concentrations of drugs within the CNS **(CIII)**. If CSF HIV resistance testing is not available, the regimen may be changed based on the patient's treatment history or on predicted drug penetration into the CNS **(CIII)**.[68-71]

This "neurosymptomatic" CNS viral escape should be distinguished from:

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation that is usually transient with low levels of CSF HIV RNA, likely equivalent to plasma blips;[72,73] *or*
- A transient increase in CSF HIV RNA that is related to other CNS infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster[74]).

There does not appear to be an association between these asymptomatic CSF HIV RNA elevations and the relatively common chronic, usually mild, neurocognitive impairment in patients with HIV who show no evidence of CNS viral breakthrough.[75] Unlike the "neurosymptomatic" CNS viral escape, these latter conditions do not currently warrant a change in ART.[76]

Summary

The management of treatment-experienced patients with virologic failure often requires expert advice to construct virologically suppressive regimens. Before modifying a regimen, it is critical to carefully evaluate the potential cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug and food interactions, as well as review HIV RNA and CD4 cell count changes over time, complete treatment history, and current and previous drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider the use of investigational agents through participation in clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

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Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel's Recommendations

- Morbidity and mortality from several AIDS and non-AIDS conditions are increased in individuals with HIV despite antiretroviral therapy (ART)-mediated viral suppression, and are predicted by persistently low CD4 T lymphocyte (CD4) cell counts and/or persistent immune activation.
- ART intensification by adding antiretroviral (ARV) drugs to a suppressive ART regimen does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(AI)**.
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended **(BIII)**.
- No interventions designed to increase CD4 cell counts and/or decrease immune activation are recommended at this time (in particular, interleukin-2 **is not recommended [AI]**) because no intervention has been proven to decrease morbidity or mortality during ART-mediated viral suppression.
- Monitoring markers of immune activation and inflammation **is not recommended** because no immunologically targeted intervention has proven to improve the health of individuals with abnormally high biomarker levels, and many markers that predict morbidity and mortality fluctuate widely in individuals **(AII)**.
- Because there are no proven interventions to improve CD4 cell recovery and/or inflammation, efforts should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and exercise; treating hypertension and hyperlipidemia) **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in individuals with HIV continues to be greater than in the general population, particularly when ART is delayed until advanced disease stages. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type II diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and frailty.[1] Although health-related behaviors and toxicities of antiretroviral (ARV) drugs may also contribute to the increased risk of illness and death, poor CD4 T lymphocyte (CD4) cell recovery, persistent immune activation, and inflammation likely also contribute to the risk.

Poor CD4 Cell Recovery

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most individuals with HIV will continue to increase for at least a decade. The rate of CD4 cell recovery is typically most rapid in the first 3 months of suppressive ART, followed by more gradual increases over time.[2-4] If ART-mediated viral suppression is maintained, most individuals will eventually recover CD4 counts in the normal range (>500 cells/mm^3); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm^3) may plateau at abnormally low CD4 cell counts.[3-5] Early initiation of ART in individuals with recent HIV diagnoses likely provides the best opportunity for maximal CD4 cell recovery.[6]

Persistently low CD4 cell counts despite ART-mediated viral suppression are associated with increased risk of morbidity and mortality. For example, individuals with HIV who have CD4 counts <200 cells/mm^3 despite at least 3 years of suppressive ART had a 2.6-fold greater risk of mortality than those with higher CD4 cell counts.[7] Lower CD4 cell counts during ART-mediated viral suppression are associated with an increased risk of non-AIDS morbidity and mortality,[8-11] including cardiovascular disease,[12] osteoporosis and

fractures,[13] liver disease,[14] and infection-related cancers.[15] The prognostic importance of higher CD4 cell counts likely spans all ranges of CD4 cell counts, though incremental benefits are harder to discern once CD4 counts increase to >500 cells/mm^3.[16]

Individuals with poor CD4 cell recovery should be evaluated for modifiable causes of CD4 cell lymphopenia. Concomitant medications should be reviewed, with a focus on those known to decrease white blood cells or, specifically, CD4 cells (e.g., cancer chemotherapy, interferon, zidovudine,[17] or the combination of tenofovir disoproxil fumarate [TDF] and didanosine [ddI]).[18,19] If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., HCV, HIV-2) and serious medical conditions (e.g., malignancy) should also be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and/or in those with CD4 counts consistently below 100 cells/mm^3. In many cases, no obvious cause for suboptimal immunologic response can be identified.

Despite strong evidence linking low CD4 cell counts and increased morbidity during ART-mediated viral suppression, no adjunctive therapies that increase CD4 cell count beyond levels achievable with ART alone have been proven to decrease morbidity or mortality. Adding ARV drugs to an already suppressive ART regimen does not improve CD4 cell recovery,[20-25] and does not reduce morbidity or mortality. Therefore, ART intensification is not recommended as a strategy to improve CD4 cell recovery **(AI)**. In individuals maintaining viral suppression, switching ARV drug classes in a suppressive regimen also does not consistently improve CD4 cell recovery and is not recommended **(BIII)**.[26] Two large clinical trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2, an immune-based therapy, in improving CD4 cell recovery. Interleukin-2 adjunctive therapy resulted in CD4 cell count increases but with no observable clinical benefit. Therefore, interleukin-2 **is not recommended (AI)**.[27] Other immune-based therapies that increase CD4 cell counts (e.g., growth hormone, interleukin-7) are under investigation. However, none of the therapies have been evaluated in clinical endpoint trials; therefore, whether any of these approaches will offer clinical benefit is unclear. Currently, such immune-based therapies should not be used except in the context of a clinical trial.

Persistent Immune Activation and Inflammation

Although poor CD4 cell recovery likely contributes to morbidity and mortality during ART-mediated viral suppression, there is increasing focus on persistent immune activation and inflammation as potentially independent mediators of risk. HIV infection results in heightened systemic immune activation and inflammation, effects that are evident during acute infection, persist throughout chronic untreated infection, and predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels.[28] Although immune activation declines with suppressive ART, it often persists at abnormal levels in many individuals with HIV maintaining long-term ART-mediated viral suppression—even in those with CD4 cell recovery to normal levels.[29,30] Immune activation and inflammatory markers (e.g., IL-6, D-dimer, hs-CRP) also predict mortality and non-AIDS morbidity during ART-mediated viral suppression, including cardiovascular and thromboembolic events, cancer, neurocognitive dysfunction, and frailty.[28] Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm^3) tend to have greater immune activation and inflammation than those with greater recovery,[29] the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count.[31,32] Even in individuals with CD4 counts >500 cells/mm^3, there is evidence that immune activation and inflammation contribute to morbidity and mortality.[33] Thus, innate immune activation and inflammation are potentially important targets for future interventions.

Although the drivers of persistent immune activation during ART are not completely understood, HIV persistence, coinfections, and microbial translocation likely play important roles.[28] Interventions to reduce each of these presumed drivers are currently being investigated. Importantly, adding ARV drugs to an already suppressive ART regimen (ART intensification) does not consistently improve immune activation.[20-23,25]

Although some studies have suggested that switching an ART regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,[34,35] these studies have limitations and results are not consistent across markers and among studies. Thus, at this time, ART modification cannot be recommended as a strategy to reduce immune activation **(BIII)**. Other commonly used medications with anti-inflammatory properties (e.g., statins, aspirin) are being studied, and preliminary evidence suggests that some may reduce immune activation in treated HIV infection.[36,37] However, because no intervention specifically targeting immune activation or inflammation has been studied in a clinical outcomes trial in treated HIV infection, no interventions to reduce immune activation are recommended at this time.

In the absence of proven interventions, there is currently no clear rationale to monitor levels of immune activation and inflammation in treated HIV infection. Furthermore, many of the inflammatory markers that predict morbidity and mortality fluctuate significantly in individuals with HIV. Thus, clinical monitoring with immune activation or inflammatory markers **is not currently recommended (AII)**. The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities such as hypertension, hyperlipidemia, and diabetes **(AII)**.

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Optimizing Antiretroviral Therapy in the Setting of Viral Suppression (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommedations

- Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations.
- The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options **(AI)**.
- It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results, before selecting a new antiretroviral therapy regimen **(AI)**.
- Adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt a regimen switch. Within-class and between-class switches can usually maintain viral suppression, provided that there is no viral resistance to the ARV agents in the new regimen **(AI)**.
- Monotherapy with either a boosted protease inhibitor or an integrase strand transfer inhibitor has been associated with unacceptable rates of virologic failure and the development of resistance; therefore, monotherapy as a switching strategy **is not recommended (AI)**.
- When switching an ARV regimen in a person with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV infection should be continued. Discontinuation of HBV drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage.
- Consultation with an HIV specialist should be considered when planning a regimen switch for a patient with a history of resistance to one or more drug classes **(BIII)**.
- Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

With currently available antiretroviral therapy (ART), most patients living with HIV can achieve and maintain HIV viral suppression. Furthermore, advances in treatment and a better understanding of drug resistance make it possible to consider switching from an effective regimen to another regimen in some situations (see below). When considering such a switch, clinicians must keep several key principles in mind in order to maintain viral suppression while addressing the concerns with the current regimen.

Reasons to Consider Regimen Switching in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 16 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see the Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Switching

Maintain Viral Suppression

The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options **(AI)**. If a regimen switch results in virologic failure with the emergence of new resistance

mutations, the patient may require more complex or expensive regimens.

Careful Review of Antiretroviral History Before Switch

The review of a patient's full antiretroviral (ARV) history—including virologic responses, past ARV-associated toxicities, and cumulative resistance test results—is warranted before any treatment switch **(AI)**. If a patient with pre-ART wild-type HIV achieves and maintains viral suppression after ART initiation, one can assume that no new resistance mutation emerged while the patient was on the suppressive regimen.

Assess Prior Resistance Before Switch

Review of cumulative resistance test results is essential when designing a new regimen. Cumulative resistance test results refer to all previous and currently available results from standard genotype, proviral DNA genotype, phenotype, and tropism assays that can be used to guide the selection of a new regimen. Once selected, a resistance mutation is generally archived in the HIV reservoir and is likely to re-emerge under the appropriate selective drug pressure, even if it is not detected in the patient's most recent resistance test. When resistance data are not available, resistance may often be inferred from a patient's treatment history. For example, a patient who experienced virologic failure on a lamivudine (3TC)-containing regimen or an emtricitabine (FTC)-containing regimen in the past is likely to have the M184V substitution, even if it is not documented. For patients with documented failure on a regimen that contains elvitegravir (EVG), raltegravir (RAL), or a non-nucleoside reverse transcriptase inhibitor (NNRTI), resistance to these drugs should be assumed because these drugs generally have a lower barrier to resistance than other ARV drugs. If there is uncertainty about prior resistance, it is generally not advisable to switch a suppressive ARV regimen unless the new regimen is likely to be at least as active against potential resistant virus as the suppressive regimen. This is particularly applicable when switching ARV-experienced individuals from a regimen with a high barrier to resistance to one with a lower barrier to resistance.[1] Consulting an HIV specialist is recommended when contemplating a regimen switch for a patient with a history of resistance to one or more drug classes **(BIII)**.

If switching is considered in patients with suppressed viral loads who do not have prior resistance data, next-generation proviral DNA genotypic resistance testing can be considered. For patients who have no prior virologic failures and who are on their first or second regimen, or those who have genotypic test results from prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide useful information. In individuals with multiple prior failures or a history of multiple prior ARV regimens, the use of proviral DNA genotypic testing may be useful. However, the results must be interpreted with caution, as these assays may not detect all of a patient's drug resistance mutations, especially those that were selected by a previous ART regimen. In addition, these assays may identify mutations that appear to be inconsistent with a patient's response to treatment, making the clinical relevance of the assay results questionable. Overall, the clinical utility of these assays remains an area of active investigation (see Drug-Resistance Testing).

Switching in a Person with Hepatitis B Virus Coinfection

When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) should be continued as part of the new regimen, unless these drugs are contraindicated. Both TDF and TAF are active against HBV infection.[2] Discontinuation of these drugs may lead to reactivation of HBV, which may result in serious hepatocellular damage. Using 3TC or FTC as the only active drug for HBV infection **is not recommended**, as HBV resistance to these drugs can emerge rapidly. If TDF or TAF cannot be used as part of the ARV regimen, refer to Hepatitis B Virus/HIV Coinfection for recommendations.

Assess for Potential Drug Interactions

Before switching a regimen, it is important to review the ARV drugs in the new regimen and concomitant medications to assess whether there are any potential drug-drug interactions. For example, rilpivirine (RPV) may interact with acid-lowering agents, and TAF and bictegravir (BIC) may interact with rifamycins (see

Drug-Drug Interactions). In addition to new drug interactions, the discontinuation of some ARV drugs may also necessitate adjusting the dosage of concomitant medications. For example, discontinuation of pharmacokinetic boosters (ritonavir or cobicistat) may reduce the concentrations of some concomitant medications. Concomitant medications which may have previously been managed with dose adjustments will need to be re-evaluated in the context of the new ART regimen.

Assess for Potential for Pregnancy

A pregnancy test should be performed for those of childbearing potential prior to switching ART. If a person with HIV is found to be pregnant, clinicians should refer to the Perinatal Guidelines for recommendations on the safety and efficacy of ARV use in pregnancy. Preliminary data from Botswana suggest there may be an increased risk of neural tube defects (NTDs) in infants born to women who were receiving dolutegravir (DTG) at the time of conception.[3,4]

Until more information is available:

- Clinicians should discuss the possible association between NTDs and DTG use during conception and the benefits of DTG for HIV treatment with individuals of childbearing potential; clinicians should also provide appropriate counseling so that the individual can make an informed decision about the use of DTG **(AIII)**.
- DTG **is not recommended** for those:
  - Who are pregnant and within 12 weeks post-conception;
  - Who are of childbearing potential, sexually active, and not using effective contraception; *or*
  - Who are contemplating pregnancy.
- It is unknown whether the possible risk of NTDs associated with DTG use at the time of conception is shared by other integrase strand transfer inhibitors (INSTIs) (i.e., a class effect).
- BIC is structurally similar to DTG, but 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 taken before considering BIC-containing ART.

Monitoring after Switch

Close monitoring to assess tolerability, viral suppression, adherence, and safety is recommended during the first 3 months after a regimen switch (see below).

Specific Regimen Switching Considerations (also see Adverse Effects of Antiretroviral Agents)

As with ART-naive patients, the use of a three-drug combination regimen is generally recommended when switching patients with suppressed viral loads to a new regimen. Patients with no resistance mutations can likely switch to any regimen that has been shown to be highly effective in ART-naive patients. In addition, there is growing evidence that certain two-drug regimens can maintain virologic suppression, as discussed below. Monotherapy with either a boosted protease inhibitor (PI) or an INSTI has been explored in several trials or cohort studies. Monotherapy has been associated with a higher rate of virologic failure than other regimens and has been associated with the development of resistance, especially INSTI monotherapy; therefore, monotherapy as a switching strategy **is not recommended (AI)**.

Strategies with Good Supporting Evidence

Three-Drug Regimens

Within-Class Switches

Within-class switches that are prompted by adverse events or the availability of ARVs within the same class

that offer a better safety profile, reduced dosing frequency, higher barrier to resistance, or lower pill burden usually maintain viral suppression, provided there is no drug resistance to the new ARV. Some examples of within-class switch strategies are switching from:

- TDF[5,6] or abacavir (ABC)[7] to TAF
- RAL to elvitegravir/cobicistat (EVG/c)[8] or DTG
- DTG[9,10], EVG/c, or RAL to BIC
- Efavirenz (EFV) to RPV[6,11]
- A ritonavir-boosted PI (PI/r) to a PI coformulated with cobicistat (PI/c)
- Boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with ABC/3TC)[12-14]

Between-Class Switches

Between-class switches generally maintain viral suppression, provided there is no resistance to the other components of the regimen. Such switches should be avoided if there is any doubt about the activity of the other agents in the regimen. As noted earlier, prior resistance test results will be very informative in guiding this switch.

Some examples of between-class switch strategies are:

- Replacing a boosted PI with an INST (e.g., DTG,[15] BIC,[16] or EVG[17,18])
- Replacing a boosted PI with RPV[19]
- Replacing an NNRTI with an INSTI[20,21]
- Replacing a boosted PI with maraviroc (MVC).[22] When switching to MVC, co-receptor usage in patients with virologic suppression can be determined from proviral DNA (see Co-receptor Tropism Assays) obtained from peripheral blood mononuclear cells.[22-24]

Two-Drug Regimens

There is growing evidence that some two-drug regimens are effective in maintaining virologic control in patients who initiated therapy and achieved virologic suppression with three-drug regimens. However, caution should be taken in patients with HBV coinfection, as these simplified regimens may not have adequate anti-HBV activity. Below are examples of successful strategies for switching from three- to two-drug regimens in persons with suppressed HIV.

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for ≥1 year and no history of virologic failure.[25] Participants were randomized to stay on their combination ART regimen or to switch to a regimen of once-daily DTG plus RPV. Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. DTG plus RPV is available as a coformulated single-tablet regimen. This regimen is a reasonable option when the use of nucleoside reverse transcriptase inhibitors (NRTIs) is neither desirable nor necessary. It should only be given to patients who do not have chronic HBV infection, have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce either drug's concentration **(AI)**.

Ritonavir-Boosted Protease Inhibitor plus Lamivudine or Emtricitabine

There is growing evidence that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, who achieved sustained viral suppression for ≥1 year, and who have no evidence of, or risk of resistance to, either the PI/r or 3TC. A PI/r plus 3TC/FTC may be a reasonable option when the

continued use of TDF, TAF, or ABC is contraindicated or not desirable. Examples of boosted PI plus 3TC regimens which have been studied in clinical trials include the following:

- ATV/r plus 3TC **(CI)**,[26,27]
- Darunavir/ritonavir (DRV/r) plus 3TC **(BI)**,[28] *or*
- Lopinavir/ritonavir (LPV/r) plus 3TC **(CI)**.[29]

Strategies for Patients with Viral Suppression and a History of Treatment Failure

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

The combination of EVG/c/TAF/FTC plus DRV has been shown to be a potential simplification strategy in patients with complicated salvage regimens.[30] A randomized controlled trial enrolled 135 virologically suppressed patients who were receiving DRV-containing ART and had resistance to at least two ARV drug classes, but no INSTI resistance. Eligible participants could have up to three thymidine analog resistance mutations and/or the K65R mutation, but no history of either the Q151M mutation or T69 insertion mutations. The patients were randomized 2:1 to either switch to a regimen of EVG/c/TAF/FTC plus DRV or remain on their original regimen. At 24 weeks, 97% of the patients in the EVG/c/TAF/FTC plus DRV arm maintained virologic suppression. The pill burden was reduced from an average of five tablets per day to two tablets per day. This regimen would be an appropriate option for individuals with similar treatment and drug resistance histories as those included in this study **(AI)**.

Strategies with Some Supporting Evidence

Other switching strategies in patients with viral suppression have some evidence to support their use. These strategies cannot be recommended until further evidence is available. If used, patients should be closely monitored to assure that viral suppression is maintained. Some of these strategies are listed below.

Boosted Protease Inhibitor plus Integrase Strand Transfer Inhibitor

In two small observational studies (which included 13 participants and 56 participants) in which participants were switched from their current ART regimens to DRV/r plus DTG, viral suppression was maintained in over 97% of the patients for a mean of 12.8 months in the first cohort and at 48 weeks in the second cohort.[31,32]

Dolutegravir plus Lamivudine

A switch to DTG plus 3TC as maintenance strategy in patients with viral suppression has been examined in two small clinical trials and in two observational studies.

Clinical Trials

The LAMIDOL trial evaluated a regimen of DTG and 3TC as a maintenance strategy in patients with virologic suppression who had no evidence of NRTI, INSTI, or PI resistance.[33] At 24 weeks, 103 of the 104 participants remained virologically suppressed.

The ASPIRE study included 90 participants with viral suppression on three-drug ART and no history of virologic failure. These participants were randomized to remain on their current regimen or to switch to DTG plus 3TC. The DTG plus 3TC regimen was noninferior to continuing the three-drug ART regimens (91% vs. 89% of participants remained virologically suppressed by Week 48, respectively).[34]

Observational Studies

A prospective observational study included 94 patients with viral suppression who were switched to DTG plus 3TC and who maintained viral suppression for 24 weeks following the switch.[35] Another study evaluated the safety and efficacy of this regimen in 206 patients who switched due to either drug toxicity or a desire to simplify their regimens. At Week 48, the estimated probability of maintaining viral suppression was 98.2%; at Week 96, the estimated probability was 95.1%.[36]

Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy

The strategy of switching patients with virologic suppression without PI resistance from one ART regimen to PI/r monotherapy has been evaluated in several studies. The rationale for this strategy is to avoid NRTI toxicities and decrease costs while taking advantage of the high barrier to resistance of PIs. PI/r monotherapy maintains virologic suppression in most patients, but at lower rates than regimens that include one or two NRTIs.[37-39] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy than with regimens that include one or two NRTIs. In most studies, resuming NRTIs in patients who are experiencing low-level viral rebound has led to re-suppression.[40-43] No clinical trials evaluating the use of coformulated PI/c regimens as monotherapy or comparing different PI/r monotherapy regimens have been conducted. On the basis of the results from these studies, boosted PI monotherapy **is not recommended (AI)**.

Dolutegravir Monotherapy

The strategy of switching virologically suppressed patients to DTG monotherapy has been evaluated in cohort studies and in clinical practice,[44,45] as well as in a randomized controlled trial.[46] This strategy has been associated with an unacceptable risk of virologic failure and subsequent development of INSTI resistance; therefore, it **is not recommended (AI)**.

Boosted Atazanavir plus Raltegravir

In a randomized study, virologically suppressed patients switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. The ATV/r plus RAL regimen switch was associated with higher rates of virologic failure and treatment discontinuations than switching to ATV/r plus TDF/FTC.[47] A regimen consisting of ATV/r plus RAL cannot currently be recommended **(AI)**.

Maraviroc plus Boosted Protease Inhibitor

In a randomized controlled trial, virologically suppressed patients who were on a regimen of two NRTIs plus a boosted PI and who had only CCR5-tropic HIV (as detected by proviral DNA testing) were randomized to continue their present regimen or to switch to MVC plus two NRTIs or to MVC plus a boosted PI. The boosted PI plus MVC regimen switch was associated with higher rates of virologic failure and treatment discontinuations than the other two regimens. Based on these results, a regimen consisting of a boosted PI and MVC cannot be recommended **(AI)**.[48]

Maraviroc plus Raltegravir

In a nonrandomized pilot study, virologically suppressed patients were switched from their prescribed regimen to MVC plus RAL. This combination led to virologic relapse in five out of 44 patients.[49] On the basis of these study results, use of a combination of MVC and RAL **is not recommended (AII)**.

Monitoring after Treatment Changes

After a treatment switch, patients should be evaluated closely for 3 months (e.g., a clinic visit or phone call 1 to 2 weeks after the change and a viral load test to check for rebound viremia 4 to 8 weeks after the switch) **(AIII)**. The purpose of this close monitoring is to assess medication tolerance and conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or if there are potential concerns with the new regimen. For example, if lipid abnormalities were present and were a reason for the ARV change, or if lipid abnormalities are a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring).

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Discontinuation or Interruption of Antiretroviral Therapy (Last updated April 8, 2015; last reviewed April 8, 2015)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression.[1-5] Thus, planned interruptions of ART are not generally recommended. However, unplanned interruption of ART may occur under certain circumstances as discussed below.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or interrupted access to drugs. Stopping ART for a short time (i.e., less than 1 to 2 days) because of a medical/surgical procedure can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Short-Term Therapy Interruption

When a Patient Experiences a Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications:

- All components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short-Term Therapy Interruption (Up to 2 Weeks)

When All Regimen Components Have Similar Half-Lives and Do Not Require Food for Proper Absorption:

- All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.

When All Regimen Components Have Similar Half-Lives and Require Food for Adequate Absorption, and the Patient Cannot Take Anything by Mouth for a Short Time:

- Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

When the Antiretroviral Regimen Contains Drugs with Different Half-Lives:

- Stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]), which may increase the risk of selection of NNRTI-resistant mutations. Some experts recommend stopping the NNRTI first and the other antiretroviral drugs 2 to 4 weeks later. Alternatively, the NNRTI may be replaced with a ritonavir- or cobicistat-boosted protease inhibitor (PI/r or PI/c) for 4 weeks. The optimal time sequence for staggered discontinuation of regimen components, or replacement of the NNRTI with a PI/r or PI/c, has not been determined.

Planned Long-Term Therapy Interruptions

Planned long-term therapy interruptions are **not recommended** outside of controlled clinical trials **(AI)**. Several research studies are evaluating approaches to a functional (virological control in the absence of therapy) or sterilizing (virus eradication) cure of HIV infection. Currently, the only way to reliably test the effectiveness of these strategies may be to interrupt ART and closely monitor viral rebound over time in the setting of a clinical trial.

If therapy must be discontinued, patients should be aware of and understand the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for

chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

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Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early) HIV Infection (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection **(AI)**, including those with early[a] HIV-1 infection.
- Once initiated, the goal of ART is to suppress plasma HIV-1 RNA to undetectable levels **(AIII)**. Testing for plasma HIV-1 RNA levels, CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as recommended for patients with chronic HIV-1 infection **(AII)**.
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**.
- ART can be initiated before drug resistance test results are available. Either boosted darunavir (DRV) or dolutegravir (DTG) with emtricitabine (FTC) plus either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are recommended regimens in this setting **(AIII)**. The rationales and precautions for these regimens are discussed below.
- A DRV-based regimen is a good option for people with early HIV-1 infection, because resistance to pharmacokinetically enhanced protease inhibitors (PIs) emerges slowly and clinically significant transmitted resistance to PIs is uncommon.
- A DTG-based regimen is also a reasonable option; however, data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of DTG regimens in early HIV infection are more limited **(AIII)**.
- Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects. Until more information are available, DTG **should not be prescribed** for individuals:
  - Who are pregnant and within 12 weeks post-conception;
  - Who are of childbearing potential, who are sexually active, and who are not using effective contraception; or
  - Who are contemplating pregnancy.
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted **(AII)**. In patients without transmitted drug-resistant virus, therapy should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.
- Patients starting ART should be willing and able to commit to life-long treatment and should understand the importance of adherence **(AIII)**. Patients may choose to postpone ART, and providers, on a case-by-case basis, may recommend that patients defer therapy because of clinical or psychosocial factors.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

[a] Early infection represents either acute or recent infection.

Definitions: Acute HIV-1 infection, the phase of HIV-1 disease that occurs immediately after transmission, is typically characterized by an initial burst of viremia; although anti-HIV-1 antibodies are undetectable during this phase, HIV-1 RNA or p24 antigen are present. Recent infection is generally considered the phase up to 6 months after infection, during which detectable anti-HIV-1 antibodies develop. Throughout this section, the term "early HIV-1 infection" is used to refer to either acute or recent HIV-1 infection.

Although some patients with acute HIV-1 infection experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms,[1-6] a recent prospective study shows that most patients have nonspecific and relatively mild signs and symptoms.[7] Primary care clinicians may fail to recognize acute HIV-1 infection because its manifestations are often similar to those of many other viral infections, such as influenza and infectious mononucleosis. Acute infection can also be asymptomatic. Table 12 provides practitioners with guidance to recognize, diagnose, and manage acute HIV-1 infection.

Diagnosing Acute HIV-1 Infection

Health care providers should consider a diagnosis of acute HIV-1 infection in patients who have a suggestive clinical syndrome—especially those who report recent high-risk behavior (see Table 12).[8] Patients may not always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV-1 acquisition. Thus, even in the absence of reported high-risk behaviors, practitioners should have a low threshold for considering a diagnosis of acute HIV-1 infection, especially in high-prevalence areas (areas where ≥1% of people have HIV infection). Current statistics on the prevalence of HIV in different geographical areas in the United States can be found at these websites: AIDSVu and the Centers for Disease Control and Prevention (CDC)'s AtlasPlus.

Acute HIV-1 infection is usually defined as detectable HIV-1 RNA or p24 antigen in serum or plasma in the setting of a negative or indeterminate HIV-1 antibody test result.[8,9] Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (often referred to as fourth-generation assays) are now approved by the Food and Drug Administration. The most recent CDC testing algorithm recommends these assays as the preferred assays to use for HIV screening, including in cases of possible acute HIV-1 infection. Specimens that are reactive on an initial antigen/antibody (Ag/Ab) assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies.[10] Specimens that are reactive on the initial assay and have either negative or indeterminate antibody differentiation test results should be tested for quantitative or qualitative HIV-1 RNA; an undetectable HIV-1 RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV-1 RNA in this setting indicates that acute HIV-1 infection is highly likely.[10] HIV-1 infection should be confirmed later by subsequent testing to document HIV antibody seroconversion.

Some health care facilities may still be following HIV testing algorithms that recommend initial testing with an assay that only tests for anti-HIV antibodies. In such settings, when acute HIV-1 infection is suspected in a patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV-1 RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV-1 RNA test result indicate that acute HIV-1 infection is highly likely. Providers should be aware that a low-positive quantitative HIV-1 RNA level (e.g., <10,000 copies/mL) may represent a false-positive result, because HIV-1 RNA levels in acute infection are generally (but not always) very high (e.g., >100,000 copies/mL).[5-7] Therefore, when a low-positive quantitative HIV-1 RNA test result is obtained, the HIV-1 RNA test should be repeated using a different specimen from the same patient, because repeated false-positive HIV-1 RNA tests are unlikely.[6] The diagnosis of HIV-1 infection should be confirmed by subsequent documentation of HIV antibody seroconversion (see Table 12).

Treating Early HIV-1 Infection

Clinical trial data regarding the treatment of early HIV-1 infection are limited. However, a number of studies suggest that individuals who are treated during early infection may experience immunologic and virologic benefits.[11-19] In addition, because early HIV-1 infection is often associated with high viral loads and increased infectiousness,[20] and the use of antiretroviral therapy (ART) by individuals with HIV reduces the risk of transmission to sexual partners without HIV,[21] treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission.

The START and TEMPRANO trials evaluated the timing of ART initiation (see Initiation of Antiretroviral Therapy). Although neither trial collected specific information on patients with early infection, the strength of the two studies' overall results and the evidence from the other studies described above strongly suggest that, whenever possible, patients should begin ART upon diagnosis of early infection.

Considerations When Treating Early HIV-1 Infection

As with chronic infection, patients with early HIV-1 infection must be willing and able to commit to life-long ART. On a case-by-case basis, providers may recommend that patients defer therapy for clinical or

psychosocial reasons. If ART is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready. Patients should also be reminded regularly of the importance of using condoms consistently and correctly during sex. The consistent use of condoms will reduce a patient's risk of transmitting HIV infection or being re-infected and help them to avoid exposure to sexually transmitted infections (see the CDC's fact sheets on condom effectiveness).

Treating Early HIV-1 Infection During Pregnancy

All patients of childbearing potential who receive a diagnosis of early HIV-1 infection should have a pregnancy test. Because early HIV-1 infection, especially in the setting of high-level viremia, is associated with a high risk of perinatal transmission, all pregnant women with HIV-1 infection should start combination ART as soon as possible to prevent perinatal transmission of HIV-1.[22]

Treatment Regimens for Early HIV-1 Infection

Prior to the widespread use of integrase strand transfer inhibitors (INSTIs), data from the United States and Europe demonstrated that transmitted virus may be resistant to at least one antiretroviral (ARV) drug in up to 16% of patients.[23,24] In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least one drug.[25] Therefore, before initiating ART in a person with early HIV-1 infection, a specimen for genotypic ARV drug resistance testing should be obtained and the results of the test should be used to help guide selection of an ARV regimen **(AII)**. However, treatment initiation itself should not be delayed pending resistance testing results. Once the resistance test results are available, the treatment regimen can be modified, if warranted **(AII)**.

As in chronic infection, the goal of ART during early HIV-1 infection is to suppress plasma HIV-1 RNA to undetectable levels **(AIII)**. ART should be initiated with one of the combination regimens recommended for patients with chronic infection **(AIII)** (see What to Start). If available, the results of ARV drug resistance testing or the ARV resistance pattern of the source person's virus should be used to guide selection of the ARV regimen.

If ART will be initiated before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen is an appropriate choice (e.g., boosted darunavir [DRV] plus either tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF] with emtricitabine [FTC]), because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon **(AIII)**.

Dolutegravir (DTG) plus TAF/FTC or TDF/FTC can also be used in certain patients **(AIII)**. Although data regarding the efficacy of a DTG-based regimen in persons with acute/early HIV infection are limited, there are several reasons why DTG is a good treatment option—transmission of DTG-resistant HIV is rare, and DTG's barrier to resistance exceeds that of raltegravir (RAL) and elvitegravir (EVG). On the basis of data from *in vitro* studies and clinical trials in ART-naive patients, it is anticipated that, like DTG, bictegravir (BIC) has a high barrier to resistance. However, clinical data and experience are relatively limited at this time.

Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects.[26,27] DTG is therefore **not recommended** for persons with acute/early HIV who are pregnant and within 12 weeks post-conception **(AII)**. DTG is also not recommended for individuals of childbearing potential who are sexually active and cannot use effective contraception or who are contemplating pregnancy **(AII)**. These patients should receive a boosted PI-based regimen. It is unknown whether this possible risk of neural tube defects is shared by other INSTIs (i.e., whether this is a class effect). BIC is structurally similar to DTG, and there are no safety data on the use of BIC around the time of conception. For individuals who are of childbearing potential and who are not pregnant, an approach similar to that outlined for DTG should be taken before considering BIC-containing ART.

Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Abacavir/lamivudine is not recommended as part of an empiric treatment of acute infection unless the patient is known to be HLA-B* 5701 negative—information that is seldom available when patients with acute infection present for care. Therefore, TDF/FTC or TAF/FTC is generally recommended as a backbone in this setting.

Given the increasing use of TDF/FTC as pre-exposure prophylaxis (PrEP) in HIV-negative individuals,[28-30] early infection may be diagnosed in some patients while they are taking TDF/FTC for PrEP. In this setting, drug resistance testing should be performed; however, as described above, use of a boosted PI (e.g., boosted DRV) or DTG plus TDF/FTC or TAF/FTC remain reasonable treatment options pending resistance testing results, while keeping in mind the caveats discussed above concerning DTG use among patients who are pregnant or of childbearing potential (see also What to Start).

Patient Follow-Up

Testing for plasma HIV-1 RNA levels, CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring (e.g., HIV-1 RNA should be assessed at initiation of ART, after 2 to 8 weeks, and then every 4 to 8 weeks until viral suppression, and thereafter, every 3 to 4 months) **(AII)**.

Duration of Therapy for Early HIV-1 Infection

Once ART is initiated in patients with early HIV infection, therapy should be continued indefinitely, following the guidelines for patients with chronic infection. A large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful, leading to increased risk of AIDS and non-AIDS events in these patients compared to those who continued ART,[31] and that this strategy was associated with increased markers of inflammation, immune activation, and coagulation.[32] For these reasons, and the potential benefit of ART in reducing the risk of HIV-1 transmission, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends indefinite continuation of ART in patients treated for early HIV-1 infection **(AIII)**.

Table 12. Identifying, Diagnosing, and Treating Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Health care providers should consider the possibility of acute HIV-1 infection in individuals with signs, symptoms, or the laboratory findings described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.[a]
  - Signs, symptoms, or laboratory findings of acute HIV-1 infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation.
  - High-risk exposures include sexual contact with a person who has HIV-1 infection or a person at risk of HIV-1 infection, sharing of injection drug use paraphernalia, or any exposure in which an individual's mucous membranes or breaks in the skin come in contact with bodily fluid that potentially carries HIV-1.
- **Differential Diagnosis:** The differential diagnosis of HIV-1 infection may include but is not limited to viral illnesses such as EBV and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.

Evaluation/Diagnosis of Acute HIV-1 Infection:

- Acute HIV-1 infection is defined as detectable HIV-1 RNA or p24 antigen (the antigen used in currently available HIV Ag/Ab combination assays) in the setting of a negative or indeterminate HIV-1 antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing to diagnose acute HIV-1 infection.
- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV-1 infection is highly likely. In this case, the diagnosis of HIV-1 infection should be later confirmed by subsequent documentation of HIV-1 antibody seroconversion.

Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all individuals with HIV-1 **(AI)** and should be offered to all patients with early HIV-1 infection.
- A pregnancy test should be performed for all individuals who receive a diagnosis of early HIV infection and who are of childbearing potential **(AIII)**.
- Pregnant patients with early HIV-1 infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV-1 **(AI)**.
- A blood sample for genotypic drug resistance testing should be obtained before initiation of ART to guide the selection of the regimen **(AII)**, but ART should be initiated as soon as possible, often prior to availability of resistance test results. If resistance is subsequently identified, treatment should be modified appropriately.
- If no resistance data are available, then a pharmacologically boosted PI-based regimen is recommended, because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. Boosted DRV (DRV/r or DRV/c) plus FTC and either TDF or TAF is a recommended regimen in this setting **(AIII)**. For similar reasons, DTG plus FTC and either TDF or TAF are reasonable options, although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited **(AIII)**.
- Preliminary data from Botswana suggested that infants born to women who were receiving DTG at the time of conception have an increased risk of neural tube defects. Until more information is available, DTG **should not be prescribed** for individuals:
  - Who are pregnant and within 12 weeks post-conception **(AII)**;
  - Who are of childbearing potential, who are sexually active, and who are not using effective contraception **(AII)**; or
  - Who are contemplating pregnancy **(AII)**.
- In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.
- Once initiated, the goal of ART should be sustained plasma virologic suppression, and ART should be continued indefinitely **(AIII)**.

[a] In some settings, behaviors that increase the risk of HIV-1 infection may not be recognized or perceived as risky by the health care provider or the patient, or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

Key to Acronyms: Ag/Ab = antigen/antibody; ART = antiretroviral therapy; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Adolescents and Young Adults with HIV (Last updated October 25, 2018; last reviewed October 25, 2018)

Key Summary and Panel's Recommendations

- Adolescents living with HIV largely belong to two distinct groups—those who acquired HIV in infancy and are heavily antiretroviral therapy (ART)-experienced, and those who acquired HIV more recently during their teens.
- ART is recommended for all individuals with HIV **(AI)** to reduce morbidity and mortality. Thus, ART is also recommended for ART-naive adolescents. Before initiation of therapy, adolescents' readiness and ability to adhere to therapy within their psychosocial context need to be carefully considered as part of therapeutic decision making **(AIII)**.
- Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression **(AII)**.
- Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects. Until more information is available, DTG should not be prescribed for adolescents:
  - Who are pregnant and within 12 weeks post-conception;
  - Who are of childbearing potential, are sexually active, and who are not using effective contraception; *or*
  - Who are contemplating pregnancy.
- The adolescent sexual maturity rating (SMR) can be helpful to guide regimen selection for initiation of or changes in ART as recommended by either these Adult and Adolescent Antiretroviral Guidelines or the Pediatric Guidelines. These Adult and Adolescent Guidelines are more appropriate for postpubertal adolescents (i.e., those with SMRs of 4 or 5) **(AIII)**.
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings. Adult providers should be sensitive to the challenges associated with such transitions, consulting and collaborating with adolescent HIV care providers to ensure adolescents' successful transition and continued engagement in care **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Older children and adolescents now make up the largest percentage of children with HIV who are cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 26% of the approximately 50,000 people newly diagnosed with HIV in 2010 were youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% were among young men who have sex with men (MSM).[1] Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV.[1] Trends in HIV/AIDS prevalence indicate that the disproportionate burden of HIV among racial minorities is even greater among minority youth 13 to 24 years of age than among those older than 24 years.[2] Furthermore, trends for all HIV diagnoses among adolescents and young adults in 46 states and 5 U.S.-dependent areas from 2007 to 2010 decreased or remained stable for all transmission categories except among young MSM. Adolescents with HIV represent a heterogeneous group in terms of socio-demographics, mode of HIV acquisition, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications to use.

Most adolescents who acquire HIV do so through sex. Many of them are recently infected and unaware of their HIV status. Many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage to and engagement in care, and initiation of ART.[3] High-grade viremia was reported in a cohort of youth living with HIV who were identified by adolescent HIV specialty clinics in 15 major metropolitan U.S. cities. The mean HIV viral load for the cohort was

94,398 copies/mL; 30% of the youth were not successfully linked to care.[4] In a study of youths with recent HIV infection, primary genotypic resistance mutations were reported in 18% of the samples, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.[5] In an ARV treatment trial, a cohort of ART-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance.[6] As these youth were naive to all ARV drugs, this reflects transmission of resistant virus. This transmission dynamic indicates that a substantial proportion of the study participants' sexual partners were likely to be older and ART-experienced; thus, using baseline resistance testing to guide initial therapy in youth who have recently acquired HIV and are naive to ART is imperative.

A limited but increasing number of adolescents with HIV are long-term survivors of HIV acquired perinatally or in infancy through blood products. These adolescents are usually heavily ART-experienced and may have a unique clinical course that differs from that of adolescents who acquire HIV later in life.[7] Adolescents who acquired HIV perinatally or in infancy were often started on ART early in life with mono- or dual-therapy regimens, resulting in incomplete viral suppression and emergence of viral resistance. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be selected on the basis of the same guiding principles used for heavily ART-experienced adults (see Virologic Failure).

Developmentally, adolescents are at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity compete with their concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and need to fit in with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage and retain adolescents in care so they can improve and maintain their health for the long term. Given the challenges of retaining youth in care and achieving long-term viral suppression,[8] more intensive case management approaches may be considered for adolescents with HIV.[9,10] Adolescents may seek care in several settings, including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.[11] When available, youth services may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents.[12] Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.[11]

Antiretroviral Therapy Considerations in Adolescents

The results from the START and TEMPRANO trials that favor initiating ART in all individuals who are able and willing to commit to treatment, and who can understand the benefits and risks of therapy and the importance of excellent adherence, are discussed elsewhere in these guidelines (see Initiation of Antiretroviral Therapy). Neither of these trials included adolescents; however, recommendations based on these trials have been extrapolated to adolescents based on the expectation that they will derive benefits from early ART that are similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of American youth with HIV, their ability to adhere to therapy needs to be carefully considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR; also known as the Tanner stage) can be helpful when ART initiation is being considered for this population (see this SMR table). Adult guidelines for ART initiation (see What to Start) or regimen changes are usually appropriate for postpubertal adolescents (SMR 4 or 5) because the clinical course of HIV infection in postpubertal adolescents who acquired HIV sexually or through injection drug use during adolescence is more similar to that in adults than that in children. Adult guidelines can also be useful for postpubertal youth who acquired HIV perinatally and whose long-term HIV infection has not affected their sexual maturity (SMR 4 or 5). Pediatric guidelines for ART may be

more appropriate for adolescents who acquired HIV during their teen years (e.g., through sex), but who are sexually immature (SMR 3 or less) and for adolescents who acquired HIV perinatally with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other comorbidities (SMR 3 or less) (see What to Start in the Pediatric Guidelines). Postpubertal youth who acquired HIV perinatally often have treatment challenges associated with the long-term use of ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects (see also Virologic Failure, Poor CD4 Cell Recovery, Optimizing Antiretroviral Therapy in the Setting of Viral Suppression, and Adverse Effects of Antiretroviral Agents). Postpubertal adolescents who acquired HIV perinatally may also have comorbid cognitive impairments that compound adherence challenges that are common among youth.[13]

Dosage of ARV drugs should be prescribed according to the SMR and not solely on the basis of age. Adolescents in early puberty (i.e., SMR 3 or less) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., SMR 4 or 5) should follow adult dosing schedules. However, SMR and age are not necessarily directly predictive of drug pharmacokinetics (PKs). Because puberty may be delayed in children with perinatally acquired HIV,[14] continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition youth from pediatric to adult doses. Youth who are in their growth spurt period (i.e., SMR 3 in females and SMR 4 in males) and who are following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in each of these circumstances to help guide therapy decisions. PK studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see the Pediatric Guidelines.[15]

Preliminary data from a study on birth outcomes among pregnant women on ART in Botswana suggested an increased rate of neural tube defects (NTDs) among infants born to women who initiated a dolutegravir (DTG)-based regimen prior to pregnancy and who were still receiving it at the time of conception.[16,17] Until more information is available, DTG is not recommended for adolescents who are pregnant and within 12 weeks post-conception. It is also not recommended for those of childbearing potential who are sexually active and not using effective contraception or those who are contemplating pregnancy.

It is not known whether this possible risk of NTDs is shared by other integrase strand transfer inhibitors (i.e., a class effect). Bictegravir (BIC) is structurally similar to DTG, but there are no safety data on the use of BIC near 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. Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Adherence Concerns in Adolescents

Adolescents with HIV are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. To meet the medical and psychosocial needs of adolescents with HIV, who frequently lack both health insurance and experience with health care systems, comprehensive systems of care are required. Studies of adolescents who acquired HIV during their teen years and adolescents with perinatal acquisition demonstrate that many adolescents in both groups face numerous barriers to adherence.[18-20] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[21] Reasons that adolescents with HIV often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV diagnosis;
- Misinformation;

- Distrust of the medical establishment;
- Fear of ART and lack of confidence in the effectiveness of medications;
- Low self-esteem;
- Unstructured and chaotic lifestyles;
- Mood disorders and other mental illness;
- Lack of familial and social support;
- Lack of or inconsistent access to care or health insurance; *and*
- Risk of inadvertent disclosure of their HIV status if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with a realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, timers, and pill boxes) that are stylish and/or inconspicuous.[22] In a randomized controlled study among nonadherent youth aged 15 years to 24 years, youth who received medication reminders through their cell phones demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls.[23] It is important to make medication adherence user-friendly and to avoid HIV-related stigma as much as possible for the older child or adolescent. Adolescents may not understand the importance of taking medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.[24-26] Directly observed therapy may be considered for some adolescents with HIV, such as those with mental illness.[27-31]

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. A young person's ability to adhere to therapy needs to be considered as part of therapeutic decision making when considering the risks and benefits of starting ART. Erratic adherence may result in the loss of future regimens due to the development of resistance mutations. Clinicians who care for adolescents with HIV frequently manage youth who pose significant concerns regarding their ability to adhere to therapy. In these cases, the following strategies can be considered:

1. A short-term deferral of ART until adherence is more likely or while adherence-related problems are aggressively addressed;
2. An adherence testing period in which a placebo (e.g., vitamin pill) is administered; *and*
3. The avoidance of any regimens with low resistance barriers.

Such decisions should ideally be individualized to reflect each patient's clinical status. For a more detailed discussion on specific therapy and adherence issues for adolescents with HIV, see Adherence to the Continuum of Care in these guidelines and the Pediatric Guidelines.[15]

Special Considerations in Adolescents

All adolescents should be screened for sexually transmitted infections (STIs), especially human papilloma virus (HPV). In young MSM, screening for STIs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.[32] For a more detailed discussion on STIs, see the most recent CDC guidelines,[33] Adult and Adolescent Opportunistic Infections Guidelines, and Pediatric Opportunistic Infections Guidelines on HPV among adolescents with HIV.[34,35] Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce those risks, should be provided to all youth. Providing gynecologic care for female adolescents with HIV is especially important. Choice of ART may also be affected by a patient's potential for pregnancy

and use of contraception, since some ARV drugs can interact with hormonal contraceptives (see Drug-Drug Interaction tables). Finally, transgender youth with HIV represent an important population that requires additional psychosocial and health care considerations. For a more detailed discussion, see Adolescent Trials Network Transgender Youth Resources.

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for children, adolescents, and young adults with HIV. A successful transition requires an awareness of the fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referring the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considering areas such as access to medical insurance; the adolescent's degree of independence/autonomy and decisional capacity; patient confidentiality; and informed consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less-motivated patients. As an additional complication to this transition, adolescents with HIV belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial considerations and needs:

- Adolescents who acquired HIV perinatally, who likely have a longer history of disease burden, complications, and chronicity; less functional autonomy; a greater need for ART; and a higher mortality risk; and
- Youth who more recently acquired HIV during their adolescence, who are likely to be in earlier stages of HIV infection and have higher CD4 T lymphocyte cell counts; these adolescents would be less likely to have viral drug resistance and may benefit from simpler treatment regimen options.

Interventions to facilitate transition should be implemented early to ensure a successful transition.[38] These interventions include the following:

- Developing an individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between adolescent and adult clinics;
- Identifying adult care providers that are willing to care for adolescents and young adults;
- Addressing patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles;
- Helping youth develop life skills, including counseling them on the appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and the importance of self-efficacy in managing medications, insurance, and assistance benefits;
- Identifying an optimal clinic model based on specific needs (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Implementing ongoing evaluation to measure the success of a selected clinic model;
- Engaging adult and adolescent care providers in regular multidisciplinary case conferences;
- Implementing interventions that may improve outcomes, such as support groups and mental health consultation;
- Incorporating a family planning component into clinical care; *and*
- Educating HIV care teams and staff about transitioning.

Discussions regarding transition should begin early, before the actual transition process.[37] Attention to the key interventions noted above will likely improve adherence to appointments and allow the youth to be retained in care. For a more detailed discussion on specific topics on transitioning care for adolescents and young adults, see HIV Clinical Guidelines Program's Adolescent Transition to Adult Care.

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HIV and People Who Use Illicit Drugs (Last updated March 27, 2012; last reviewed March 27, 2012)

Treatment Challenges in People with HIV Who Use Illicit Drugs

Injection drug use is the second most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate [i.e., poppers]). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among individuals who have HIV infection or who are at risk of HIV infection. The association between club drugs and high-risk sexual behavior in men who have sex with men (MSM) is strongest for methamphetamine and amyl nitrate; this association is less consistent with the other club drugs.[1]

Illicit drug use has been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes.[2] Treatment of HIV disease in people who use illicit drugs can be successful, but this group presents special treatment challenges. These challenges may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment.[3]

Underlying health problems in people who use injection and/or noninjection drugs result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis (TB), skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in people with HIV who use illicit drugs than in people who use illicit drugs and do not have HIV, due in part to respiratory, hepatic, and neurological impairments associated with HIV infection.[4] Success of antiretroviral therapy (ART) in people with HIV who use illicit drugs often depends on clinicians becoming familiar with and managing these comorbid conditions and providing overdose prevention support.

People with HIV who use illicit drugs have less access to HIV care and are less likely to receive ART than other populations.[5-6] Factors associated with low rates of ART use among people who use illicit drugs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and health care providers' lack of expertise in HIV treatment.[5-6] The typically unstable, chaotic life patterns of many people who use illicit drugs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence.[7] The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and people who use illicit drugs.[8,9] The first step in provision of care and treatment for these individuals is to recognize the existence of a substance use problem. It is often obvious that the problem exists, but some patients may hide these problem behaviors from clinicians. Assessment of a patient for a substance use disorder should be part of routine medical history taking and should be done in a professional, straightforward, and nonjudgmental manner.

Treatment Efficacy in Populations of People Who Use Illicit Drugs

Although people who use illicit drugs are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in people who use illicit drugs—when they are not actively using drugs—is similar to that seen in other populations.[10] Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se.[11] Providers need to remain attentive to the possible impact of disruptions caused by drug use on the patient both before and while receiving ART. Although many people who use illicit drugs can sufficiently control their drug use for a long enough time to benefit from care, treatment for substance use disorders is often necessary for successful HIV management.

Successful HIV treatment requires close collaboration with treatment programs for substance use disorders and proper support and attention to this population's special multidisciplinary needs. HIV care sites should be accommodating, flexible, and community-based, with experience in managing a wide array of needs for people who use drugs. HIV care sites must also have experience in developing effective strategies to promote medication adherence.[9] These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise among people with HIV who use illicit drugs.[12]

Antiretroviral Agents and Opioid Substitution Therapy

Compared with people receiving ART who do not use illicit drugs, people who use illicit drugs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal (GI), and hematologic disorders are highly prevalent among people who use injection drugs. These comorbid conditions should be considered when selecting antiretroviral (ARV) agents in this population. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended-release naltrexone are commonly used for management of opioid dependence in patients with HIV.

Methadone and Antiretroviral Therapy. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur.[13] These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. Patients and substance abuse treatment facilities should be informed of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and Antiretroviral Therapy. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is increasingly used for opioid dependence treatment. Compared with methadone, buprenorphine has a lower risk of respiratory depression and overdose. This allows physicians in primary care to prescribe buprenorphine for the treatment of opioid dependency. The flexibility of the primary care setting can be of significant value to patients with HIV and opioid addiction who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and ARV agents.[13,14] Findings from available studies show that the drug interaction profile of buprenorphine is more favorable than that of methadone.

Naltrexone and Antiretroviral Therapy. A once-monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid

detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[15]

Currently available pharmacokinetic (PK) interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine can be found in Tables 19a-d. Effective communication between HIV care providers and drug treatment programs is essential to prevent additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported.[16]

Summary

It is usually possible over time to support most people with HIV who actively use drugs such that acceptable adherence levels with ARV agents can be achieved.[17-18] Providers must work to combine all available resources to stabilize someone who actively uses drugs in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment and needle and syringe exchange programs, strategies to reduce high-risk sexual behavior, and harm-reduction strategies. A history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to those who do not use drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include need for supportive clinical sites, linkage to substance abuse treatment, and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

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Women with HIV (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all persons living with HIV to improve their health and to reduce the risk of HIV transmission to sex partners without HIV **(AI)**.
- When prescribing antiretroviral (ARV) drugs, clinicians should take into account that some ARV drugs have significant pharmacokinetic (PK) interactions with hormonal contraceptives; an alternative or additional effective contraceptive method to prevent unplanned pregnancy is recommended **(AIII)**. Switching to an ARV drug without interactions with hormonal contraceptives may also be considered **(BIII)**.
- A pregnancy test should be performed for those of childbearing potential prior to initiation of ART **(AIII)**.
- Preliminary data suggest there may be an increased risk of neural tube defects (NTD) in infants born to women who were receiving dolutegravir (DTG) at the time of conception. Until more information is available, DTG **is not recommended** for use in individuals who are pregnant and within 12 weeks post-conception and those who are contemplating pregnancy, unless there are no alternative options **(AII)**.
- Providers should discuss the potential risks and benefits of DTG with individuals of childbearing potential and provide appropriate counseling so that the individual can make an informed decision. For those who are sexually active and not using effective contraception, choosing an alternative to DTG is recommended. For those who are using effective contraception, use of a DTG-based regimen is reasonable after discussing the risks and benefits with the individual.
- Individuals who become pregnant and present for antenatal care at 12 weeks post-conception or later may initiate or continue DTG-based regimens **(CIII)**.
- In a patient with multidrug-resistant HIV who has no alternatives to DTG, the decision of whether to use DTG should be made after careful consideration of the risk of NTDs in the infant if pregnancy occurs while a patient is taking DTG, and the risks of persistent viremia in the patient and potential HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.
- During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy to reduce the risk of transmission to the fetus and newborn **(AI)**.
- When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and PK data on use during pregnancy for each agent. The risks and benefits of ARV use during pregnancy should be discussed with all individuals of childbearing potential **(AIII)** and clinicians should consult the most current Perinatal Guidelines when designing a regimen **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

This section focuses on some unique clinical and therapeutic issues to consider and basic principles to follow when caring for cisgender women living with HIV. Cisgender women are defined as women who were assigned female at birth and who identify themselves as women. Some topics discussed in this section, such as contraception, drug-drug interactions between antiretroviral (ARV) drugs and hormonal therapy, and pregnancy, also apply to transgender men (men assigned female at birth), and individuals assigned female at birth who identify as nonbinary (gender identities that are not exclusively feminine or masculine) or gender fluid (gender identity is not fixed). A new section focused on transgender health and HIV is currently in development and will be added to the Special Patient Population section soon. Clinicians who care for pregnant patients should consult the current Perinatal Guidelines for a more in-depth discussion and guidance on managing these patients.

Sex Difference Considerations in Antiretroviral Therapy

In general, studies to date have not shown sex differences in virologic responses to antiretroviral therapy (ART).[1-4] However, there are limited data showing that pharmacokinetics (PKs) for some ARV drugs may differ between men and women, possibly because of variations in factors such as body weight, plasma

volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.[5-7]

Adverse Effects

Several studies with older ARV drugs have suggested that sex may influence the frequency, presentation, and severity of some ARV-related adverse events. Most notably, women are more likely to develop severe symptomatic hepatotoxicity with nevirapine (NVP) use[8,9] and are more likely to develop symptomatic lactic acidosis with prolonged use of older nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV), stavudine, and didanosine.[10] These agents are no longer recommended for use in people with HIV in the United States; although ZDV is still administered intravenously (IV) to some patients during delivery, it is not generally recommended for long-term use.

Some studies have investigated how metabolic complications associated with ARV use differ between women and men. Over 96 weeks following initiation of ART, women with HIV are less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than men with HIV.[11,12] Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.[13-16] ART regimens that contain tenofovir disoproxil fumarate (TDF), ritonavir-boosted protease inhibitors (PI/r), or both are associated with a significantly greater loss of BMD than regimens containing other NRTIs and raltegravir.[17-20] Abacavir, NRTI-sparing regimens, and tenofovir alafenamide (a new oral tenofovir prodrug that induces less bone loss than TDF) may be considered as alternatives to the use of TDF in patients who are at risk of osteopenia or osteoporosis. Recommendations for management of bone disease in people with HIV have been published.[21]

Adults and Adolescents with HIV Who Are of Childbearing Potential

All adults and adolescents with HIV who are of childbearing potential should be offered comprehensive reproductive and sexual health counseling and care as part of routine primary medical care. Topics for discussion should include safe sex practices, reproductive desires and options for conception, the HIV status of sex partner(s), and use of effective contraception to prevent unplanned pregnancy. Counseling should also include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see the Perinatal Guidelines).

Antiretroviral Regimen Considerations When Trying to Conceive or For Individuals Who Cannot Use Effective Contraception

Efavirenz (EFV) is teratogenic in nonhuman primates. However, a meta-analysis that included data from 23 studies found no evidence for an increased risk of birth defects in infants born to women on EFV during the first trimester compared with infants born to women on other ARV drugs during the first trimester.[22] EFV can be used in individuals of childbearing potential who are not using effective contraception or who are contemplating pregnancy. Individuals who become pregnant on EFV-containing regimens should continue their current regimens.

A preliminary report from an observational surveillance study of birth outcomes among pregnant women on ART in Botswana found an increase in the risk of in neural tube defects (NTDs) in infants born to women who received dolutegravir (DTG) prior to conception. In this report, four infants born to 596 women (0.67%) who initiated a DTG-based regimen prior to pregnancy and who were still receiving that regimen at the time of conception were affected compared to 0.1% of infants born to women who received other ARV drugs.[23,24] This study is ongoing. By contrast, the same study identified no NTDs in the infants born to 116 women who initiated DTG-based regimens during the first trimester or the infants born to 396 women who initiated EFV-based regimens.[25]

DTG **is not recommended** for individuals who are pregnant and within 12 weeks post-conception. It is also **not recommended** if an individual of childbearing potential is sexually active and cannot use effective

contraception or is contemplating pregnancy, unless there is no alternative option **(AII)**. For those not known to be pregnant, a negative pregnancy test result should be documented prior to the initiation of DTG **(AIII)**. Women who are currently receiving DTG or who wish to start DTG should be counseled about the potential risk of NTDs when DTG is taken near the time of conception. In a patient with multidrug-resistant HIV who has no alternatives to DTG, the decision of whether to use DTG should be made after careful consideration of the risk of NTDs in the infant if pregnancy occurs while a patient is taking DTG, and the risks of persistent viremia in the patient and potential HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.

Reproductive Options for Serodiscordant Couples

An individual who wishes to conceive with a serodiscordant partner should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include screening and treating both partners for sexually transmitted infections (STIs), use of ART to maximally suppress and maintain the viral load of the partner with HIV, use of pre-exposure prophylaxis by the partner without HIV,[26-28] male circumcision, and/or self-insemination with the sperm of the partner without HIV during the periovulatory period of the individual with HIV.[29]

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unplanned pregnancies and perinatal transmission of HIV are an essential component of care for individuals with HIV of childbearing age. These individuals should receive ongoing counseling on reproductive issues. Regardless of hormonal contraceptive use, individuals with HIV should be advised to consistently use condoms (male or female) during sex and adhere to an HIV regimen that effectively maintains viral suppression. Both strategies are crucial to prevent transmission of HIV to partners without HIV and to protect against infection with other STIs. The following sections describe some factors to consider when hormonal contraceptives are used.

Drug-Drug Interactions

PK interactions between ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, there are limited clinical data regarding drug interactions between ARVs and hormonal contraceptives, and the clinical implications of these interactions are unclear. The magnitudes of changes in drug concentrations that may reduce contraceptive efficacy or increase the risk of adverse effects are not known for all forms of contraceptives.

- **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 19a, 19b, and 19d), which potentially decreases contraceptive efficacy or increases the risk of estrogen- or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[30] Several regimens that include a cobicistat-boosted PI, PI/r, and EVG/c decrease oral contraceptive estradiol levels.[31-34] One PK study showed that DTG did not affect ethinyl estradiol or norgestimate levels.[35] Several studies have shown that use of etravirine, rilpivirine, and NVP did not significantly affect estradiol or progestin levels in individuals with HIV using COCs.[36-38]
- **Injectable Contraceptives:** Small studies of women with HIV who were receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, lopinavir/ritonavir (LPV/r), NVP, nelfinavir (NFV), or NRTI drugs.[39-42]
- **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.[43,44] Studies of women with levonorgestrel- and etonogestrel-releasing implants reported that participants receiving EFV-based ART had decreased bioavailability of levonorgestrel and

etonogestrel.[45-47] These studies did not identify any change in hormone concentrations when the implants were used in those taking NVP[45,47] or LPV/r.[46] Similarly, two retrospective cohort evaluations conducted in Swaziland and Kenya showed an increased risk of contraceptive failure in women using contraceptive implants and receiving EFV.[48,49]

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARV drugs should not prevent clinicians from prescribing hormonal contraceptives for individuals on ART who prefer this contraceptive method. However, an alternative or additional effective contraceptive method is recommended when there are significant drug interactions between hormonal contraceptives and ARV drugs (see drug interaction Tables 19a, 19b, and 19d and the Perinatal Guidelines).

Risk of HIV Acquisition and Transmission

Studies have produced conflicting data on the association between hormonal contraception and the risk of acquisition of HIV.[50] Most of the retrospective studies were done in the setting where the partners with HIV were not taking ART. A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the partner with HIV was not receiving ART found that, compared to women who did not use hormonal contraception, those using hormonal contraception (with the majority of study participants using injectable DMPA) had a two-fold increased risk of acquiring or transmitting HIV. Higher genital HIV RNA concentrations have been found in women with HIV using hormonal contraception than in those not using hormonal contraceptives.[51] Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women using oral contraceptives in this study was insufficient to adequately assess risk. A World Health Organization expert group reviewed all available evidence regarding hormonal contraception use and HIV transmission to a partner without HIV and recommended that individuals living with HIV can continue to use all existing hormonal contraceptive methods without restriction.[52] Further research is needed to definitively determine whether hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV, particularly in the setting of ART. Regardless, the potential association of hormonal contraception use and HIV transmission in the absence of ART underscores the importance of ART-induced viral suppression to reduce transmission risk.

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for individuals with HIV.[53-55] Although studies have focused primarily on IUDs that do not contain hormones (e.g., copper IUD), several small studies have found that levonorgestrel-releasing IUDs are also safe and not associated with increased genital tract shedding of HIV.[56-58]

Pregnancy

Clinicians caring for pregnant adults and adolescents with HIV should review the Perinatal Guidelines. The use of combination ARV regimens is recommended for all pregnant persons with HIV, regardless of virologic, immunologic, or clinical parameters, for their own health and to prevent transmission of HIV to the fetus **(AI)**. Pregnant individuals with HIV should be counseled regarding the known benefits and risks of ARV use during pregnancy to the woman, fetus, and newborn. They should be counseled and strongly encouraged to receive ART for their own health and that of their infants. Open, nonjudgmental, and supportive discussion should be used to encourage them to adhere to care.

Prevention of Perinatal Transmission of HIV

The use of ART and the resultant reduction of HIV RNA levels decrease the risk of perinatal transmission of HIV.[59-61] The goal of ART is to achieve maximal and sustained viral suppression throughout pregnancy. Long-term follow-up is recommended for all infants who were exposed to ART *in utero*, regardless of the infant's HIV status (see the Perinatal Guidelines).

Antiretroviral Regimen Considerations

Pregnancy should not preclude the use of optimal ARV regimens. As in nonpregnant individuals, genotypic resistance testing is recommended for all pregnant persons before ARV initiation **(AIII)** and for those with detectable HIV RNA while on ART **(AI)**. However, ART initiation should not be delayed pending genotypic resistance test results. The ARV regimen can be modified, if necessary, once the resistance test results are available **(BIII)**. Unique considerations that influence recommendations on the ARVs to use during pregnancy include the following:

- Physiologic changes associated with pregnancy that potentially change the PKs of ARV drugs, which may affect ARV dosing at different stages of pregnancy;
- Potential ARV-associated adverse effects in pregnancy;
- Potential for nonadherence to a particular regimen during pregnancy; and
- Potential short-term and long-term effects of an ARV drug on the fetus and newborn, which are unknown for many drugs.

ART is considered the standard of care for pregnant individuals with HIV, both to treat HIV infection and prevent perinatal transmission of HIV. Clinicians should review the Perinatal Guidelines for ARV recommendations for individuals who have recently received an HIV diagnosis or those who become pregnant while on ART.

Based on preliminary data from Botswana that reported neural tube defects in infants born to women who were taking a DTG-based regimen at the time of conception, DTG **is currently not recommended** for use in those who are pregnant and within 12 weeks post-conception **(AII)**. Those who are pregnant and at 12 weeks post-conception or later may initiate or continue DTG-based regimens **(CIII)**. Discontinuing DTG is unlikely to confer any benefit after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and perinatal transmission.

If maternal HIV RNA is ≥1,000 copies/mL (or unknown) near delivery, IV infusion of ZDV during labor is recommended regardless of the mother's antepartum regimen and resistance profile and the mode of infant delivery **(AI)**. Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be administered with sips of water during this time).

Clinicians who are treating pregnant individuals with HIV are strongly encouraged to report cases of prenatal exposure to ARV drugs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry. The registry collects observational data regarding exposure to Food and Drug Administration-approved ARV drugs during pregnancy to assess potential teratogenicity.

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Because maternal ART reduces but does not eliminate the risk of transmission of HIV in breast milk and postnatal transmission can occur despite maternal ART, individuals should be counseled to avoid breastfeeding.[62] Persons with HIV should not premasticate food and feed it to their infants because the practice has been associated with mother-to-child transmission of HIV.[63] ART is currently recommended for all individuals with HIV **(AI)**; therefore, maternal ART should be continued after delivery. For more information regarding postpartum management, refer to the Perinatal Guidelines.

Several studies have demonstrated that adherence to ART may decline in the postpartum period.[64-66] Clinicians should address ART adherence at each clinic visit postpartum, including an evaluation of specific facilitators of and barriers to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to the Continuum of Care).

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HIV-2 Infection (Last updated April 8, 2015; last reviewed April 8, 2015)

Summary of HIV-2 Infection

- Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 RNA levels, and lower mortality; however, progression to AIDS does occur.
- There have been no randomized trials addressing the question of when to start antiretroviral therapy (ART) or the choice of initial or second-line therapy for HIV-2 infection; thus, the optimal treatment strategy has not been defined.
- Although the optimal CD4 T lymphocyte (CD4) cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.
- HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; thus, these drugs should not be included in an antiretroviral regimen for a patient living with HIV-2 infection.
- Pending more definitive data on outcomes in an ART-naive patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, an initial antiretroviral therapy regimen for these patients should include two nucleoside reverse transcriptase inhibitors plus an HIV-2 active boosted protease inhibitor or integrase strand transfer inhibitors.
- A few laboratories now offer quantitative plasma HIV-2 RNA testing for clinical care (see section text).
- Monitoring of HIV-2 RNA levels, CD4 cell counts, and clinical improvements can be used to assess treatment response, as is recommended for HIV-1 infection.
- Resistance-associated viral mutations to nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or integrase strand transfer inhibitors may develop in patients with HIV-2 while on therapy. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are available for clinical use.
- In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management..

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered when treating persons of West African origin or in those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France, Spain, Portugal, and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India)

Clinical Course of HIV-2 Infection

Compared to HIV-1 infection, the clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rate.[1,2] However, HIV-2 infection can also progress to AIDS over time. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from areas with a high prevalence of HIV-2.

Diagnosis of HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot.[3] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable HIV-1 RNA levels or in those with declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on antiretroviral therapy (ART).

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[4] recommend initial HIV testing using an HIV-1/HIV-2 antigen/antibody combination immunoassay and subsequent testing using an HIV-1/HIV-2 antibody differentiation immunoassay. The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration-approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2.[5,6] Quantitative HIV-2 plasma RNA viral load testing has recently become available for clinical care at the

University of Washington (http://depts.washington.edu/labweb/AboutUM/Contact.htm)[7] and the New York State Department of Health (https://www.wadsworth.org/programs/id/bloodborne-viruses/clinical-testing/hiv-2-nucleic-acid).[8] However, it is important to note that approximately one-quarter to one-third of patients with HIV-2 infection who are not on ART will have HIV-2 RNA levels below the limits of detection; some of these patients will have clinical progression and CD4 cell count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available for clinical use.

Treatment of HIV-2 Infection

To date, no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection have been completed;[9] thus, the optimal treatment strategy has not been defined. Although the optimal CD4 cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.

HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTI)[10] and to enfuvirtide (T-20).[11] Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1.[12,13] Darunavir (DRV), lopinavir (LPV), and saquinavir (SQV) are more active against HIV-2 than other approved protease inhibitors (PIs);[14-17] one of these boosted PIs should be used if a PI-based regimen is used. Other PIs should be avoided because of their lack of ARV activity and high failure rates. The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) have potent activity against HIV-2 *in vitro*.[18-21] The CCR5 antagonist maraviroc (MVC) appears active against some HIV-2 isolates;[22] however, no approved assays to determine HIV-2 co-receptor tropism exist and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[23]

Several small studies suggest poor responses in individuals with HIV-2 infection treated with some ARV regimens, including dual-NRTI regimens; regimens containing NNRTI plus two NRTIs; and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine (3TC); and atazanavir (ATV)-based regimens.[9,24-27] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[28,29] In general, HIV-2 active, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses than two or three-NRTI-based regimens.[29-31] However, CD4 cell recovery on therapy is generally poorer than that observed for HIV-1.[31-33] INSTI-based regimens may also have favorable treatment responses.[34,35] A large systematic review of ART for patients with HIV-2 infection (n = 17 studies, 976 patients with HIV-2) was unable to conclude which specific regimens are preferred.[36]

Resistance-associated viral mutations to NRTIs, PIs, and/or INSTIs commonly develop in patients with HIV-2 while on therapy.[24,29,37-41] Currently, HIV-2 transmitted drug resistance appears rare.[41,42] In one small study, DTG was found to have activity as a second-line INSTI in some patients with HIV-2 who had extensive ARV experience and RAL resistance.[43] Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ between the HIV types.[13,29,44]

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection;[45-48] however, currently, there are no controlled trial data to support the effectiveness of the recommended regimens. Pending more definitive data on outcomes in an ART-naive patient who has HIV-2 mono-infection or HIV-1/HIV-2 dual infection and requires treatment, a regimen containing two NRTIs plus an HIV-2 active boosted PI or INSTI should be initiated in individuals with HIV-2 infection.

HIV-2 plasma RNA levels, CD4 cell counts, and clinical improvements can be monitored to assess treatment response, as is recommended for HIV-1. Patients who have HIV-2 RNA levels below the limits of detection before therapy should still have HIV-2 plasma RNA monitoring, in addition to CD4 cell count and clinical monitoring. In the event of virologic, immunologic, or clinical failure, second-line treatment should be

instituted in consultation with an expert in HIV-2 management.

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HIV and the Older Patient (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Considerations When Caring for Older Patients With HIV

- Antiretroviral therapy (ART) is recommended for all patients regardless of CD4 T lymphocyte cell count (**AI**). ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART.
- Adverse drug events from ART and concomitant drugs may occur more frequently in older patients living with HIV than in younger patients with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older patients should be monitored closely.
- Polypharmacy is common in older patients with HIV; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications.
- HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older patients with HIV with complex comorbidities.
- Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older patient with HIV.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Effective antiretroviral therapy (ART) has increased survival in individuals with HIV, resulting in an increasing number of older individuals living with HIV. In the United States, among persons living with HIV at year-end 2013, 42% were age 50 years or older, 6% were age 65 or older, and trends suggest that these proportions will increase steadily.[1] Care of patients with HIV increasingly will involve adults 60 to 80 years of age, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited.

There are several distinct areas of concern regarding the association between age and HIV disease.[2] First, older patients with HIV may suffer from aging-related comorbid illnesses that can complicate the management of HIV infection. Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with advanced age. Third, reduced mucosal and immunologic defenses (such as postmenopausal atrophic vaginitis) and changes in risk related-behaviors (e.g., decrease in condom use because of less concern about pregnancy or more high-risk sexual activity with increased use of erectile dysfunction drugs) in older adults could lead to increased risk of acquisition and transmission of HIV.[3,4] Finally, because older adults are generally perceived to be at low risk of acquiring HIV, screening for this population remains low.

HIV Diagnosis and Prevention in the Older Adult

In older adults, failure to consider a diagnosis of HIV likely contributes to later initiation of ART.[5] The Centers for Disease Control and Prevention (CDC) estimates that in 2013, 37% of adults aged 55 years or older at the time of HIV diagnosis met the case definition for AIDS. The comparable CDC estimates are 18% for adults aged 25 to 34 years and 30% for adults aged 35 to 44 years.[6] In one observational cohort, older patients (defined as those ≥35 years of age) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion, steeper CD4 count decline over time,[7] and tended to present to care with significantly lower CD4 counts.[8] When individuals >50 years of age present with severe illnesses, AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Although many older individuals engage in risk behaviors associated with acquisition of HIV, they may see themselves or be perceived by providers as at low risk of infection and, as a result, they are less likely to be tested for HIV infection than younger persons.[9,10] Despite CDC guidelines recommending HIV testing at least

once in individuals aged 13 to 64, and more frequently for those at risk,[11] HIV testing prevalence remains low (<5%) among adults aged 50 to 64, and decreased with increasing age.[12] Clinicians must be attuned to the possibility of HIV infection in older adults, including those older than 64 years of age and especially in those who may engage in high-risk behaviors. Sexual history taking is therefore an important component of general health care for older adults who do not have HIV, together with risk-reduction counseling, and screening for HIV and sexually transmitted infections (STIs), if indicated.

Impact of Age on HIV Disease Progression

HIV infection presents unique challenges in aging adults and these challenges may be compounded by ART:

- HIV infection itself is thought to induce immune-phenotypic changes akin to accelerated aging,[13] but recent laboratory and clinical data provide a more nuanced view of these changes. Some studies have shown that patients with HIV may exhibit chromosomal and immunologic features similar to those induced by aging.[14,15] However, other studies show the immunologic changes to be distinct from age-related changes.[16] In addition, although data on the increased incidence and prevalence of age-associated comorbidities in patients with HIV are accumulating,[17,18] the age of diagnosis for myocardial infection and non-AIDS cancers in patients who have HIV and those who do not is the same.[18,19]
- Older patients with HIV have a greater incidence of complications and comorbidities than adults of a similar age who do not have HIV, and may exhibit a frailty phenotype—defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity,[20] although the phenotype is still incompletely characterized in people with HIV.

Initiating Antiretroviral Therapy in the Older Patient with HIV

ART is recommended for all individuals with HIV (**AI**; see Initiation of Antiretroviral Therapy section). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population. In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (patients between ages 45 and 65 years).[21] No data support a preference for any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of patient age. The choice of regimen should instead be informed by a comprehensive review of the patient's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an antiretroviral regimen based on an older patient's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older patients with reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix Table 8). In addition, ARV regimen selection may be influenced by potential interaction of antiretroviral medications with drugs used concomitantly to manage comorbidities (see Tables 19a-20b). Adults age >50 years should be monitored for ART effectiveness and safety similarly to other populations with HIV (see Table 3); however, in older patients, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, metabolic, and bone health (see Table 15).

HIV, Aging, and Antiretroviral Therapy

The efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART differs in older and younger patients. In a recent observational study, a higher rate of viral suppression was seen in patients >55 years old than in younger patients.[22] However, ART-associated CD4 cell recovery in older patients is generally slower and lower in magnitude than in younger patients.[8,23-25] This observation suggests that starting ART at a younger age may result in better immunologic response and possibly clinical outcomes.

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of

ARV drugs. Both liver and kidney functions decrease with age and may result in impaired drug elimination and increased drug exposure.[26] Most clinical trials have included only a small proportion of participants over 50 years of age, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Whether drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients is unknown.

Patients with HIV and aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management. In addition to taking medications to manage HIV infection and comorbid conditions, many older patients with HIV also are taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). They also may self-medicate with over-the-counter medicines or supplements. In older patients who do not have HIV, polypharmacy is a major cause of iatrogenic complications.[27] Some of these complications may be caused by medication errors (by prescribers or patients), medication nonadherence, additive drug toxicities, and drug-drug interactions. Older patients with HIV are probably at an even greater risk of polypharmacy-related adverse consequences than younger or similarly aged patients with HIV. When evaluating any new clinical complaint or laboratory abnormality in patients with HIV, especially in older patients, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[28] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 19a-20b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be greater in older patients with HIV than in younger patients with HIV.

Nonadherence is the most common cause of treatment failure. Complex dosing requirements, high pill burden, inability to access medications because of cost or availability, limited health literacy including misunderstanding of instructions, depression, and neurocognitive impairment are among the key reasons for nonadherence.[32] Although many of these factors associated with nonadherence may be more prevalent in older patients, some studies have shown that older patients with HIV may actually be more adherent to ART than younger patients.[29-31] Clinicians should regularly assess older patients to identify any factors, such as neurocognitive deficits, that may decrease adherence. To facilitate medication adherence, it may be useful to discontinue unnecessary medications, simplify regimens, and recommend evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members (see Adherence to the Continuum of Care).

Non-AIDS HIV-Related Complications and Other Comorbidities

Among persons treated effectively with ART, as AIDS-related morbidity and mortality have decreased, non-AIDS conditions constitute an increasing proportion of serious illnesses.[33-35] Neurocognitive impairment, already a major health problem in aging adults, may be exacerbated by the effect of HIV infection on the brain.[36] In a prospective observational study, neurocognitive impairment was predictive of lower retention in care among older persons.[37] Neurocognitive impairment probably also affects adherence to therapy. Social isolation and depression are also particularly common among older adults with HIV and, in addition to their direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.[38,39] Heart disease and cancer are the leading causes of death in older Americans.[40] Similarly, non-AIDS events such as heart disease, liver disease, and cancer have emerged as major causes of morbidity and mortality in patients with HIV receiving effective ART. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging adults with HIV.[41-43] HIV-specific primary care guidelines have been updated with recommendations for lipid and

glucose monitoring, evaluation and management of bone health, and management of kidney disease, and are available for clinicians caring for older patients with HIV.[44-48]

Switching, Interrupting, and Discontinuing Antiretroviral Therapy in Older Patients

Given the greater incidence of comorbidities, non-AIDS complications and frailty among older patients with HIV, switching one or more ARVs in an HIV regimen may be necessary to minimize toxicities and drug-drug interactions. For example, expert guidance now recommends bone density monitoring in men aged ≥50 years and postmenopausal women, and suggests switching from tenofovir disoproxil fumarate or boosted protease inhibitors to other ARVs in older patients at high risk for fragility fractures.[45]

Few data exist on the use of ART in severely debilitated patients with chronic, severe, or non-AIDS terminal conditions.[49,50] Withdrawal of ART usually results in rebound viremia and a decline in CD4 cell count. Acute retroviral syndrome after abrupt discontinuation of ART has been reported. In severely debilitated patients, if there are no significant adverse reactions to ART, most clinicians would continue therapy. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion on the risks and benefits of continuing or withdrawing ART.

Healthcare Utilization, Cost Sharing, and End-of-Life Issues

Important issues to discuss with aging patients with HIV are living wills, advance directives, and long-term care planning, including related financial concerns. Out-of-pocket health care expenses (e.g., copayments, deductibles), loss of employment, and other financial-related factors can cause temporary interruptions in treatment, including ART, which should be avoided whenever possible. The increased life expectancy and the higher prevalence of chronic complications in aging populations with HIV can place greater demands upon HIV services.[51] Facilitating a patient's continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders.

Conclusion

HIV disease can be overlooked in aging adults who tend to present with more advanced disease and experience accelerated CD4 loss. HIV induces immune-phenotypic changes that have been compared to accelerated aging. Effective ART has prolonged the life expectancy of patients with HIV, increasing the number of patients >50 years of age living with HIV. However, unique challenges in this population include greater incidence of complications and comorbidities, and some of these complications may be exacerbated or accelerated by long term use of some ARV drugs. Providing comprehensive multidisciplinary medical and psychosocial support to patients and their families (the "Medical Home" concept) is of paramount importance in the aging population. Continued involvement of HIV experts, geriatricians, and other specialists in the care of older patients with HIV is warranted.

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Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B/HIV Virus Coinfection (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel's Recommendations

- Before initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication **(AIII)**.
- Because emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have activity against both HIV and HBV, an ART regimen for patients with both HIV and HBV should be include (TAF or TDF) plus (3TC or FTC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**.
- If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen **(BI)**. Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when given to patients with HBV/HIV-coinfection **(AII)**. Peginterferon alfa monotherapy may also be considered in certain patients **(CII)**.
- Other HBV treatment regimens, including adefovir alone or in combination with 3TC or FTC and telbivudine, **are not recommended** for patients with HBV/HIV coinfection **(CII)**.
- Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against stopping these medications and be carefully monitored during interruptions in HBV treatment **(AII)**.
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment. For that reason, all patients initiating HCV therapy should be tested for HBV. Persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Approximately 5% to 10% of people with HIV in the United States also have chronic hepatitis B virus (HBV) infection.[1] The progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV coinfection than in persons with chronic HBV monoinfection.[2] Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte (CD4) cell responses following initiation of antiretroviral therapy (ART).[3,4] However, antiretroviral (ARV) drug toxicities or several liver-associated complications attributed to flares in HBV activity after initiation or discontinuation of dually active ARV drugs can affect the treatment of HIV in patients with HBV/HIV coinfection.[5-7] These complications include the following:

- Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are ARVs approved to treat HIV that are also active against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV.[8]
- The anti-HBV drug entecavir has activity against HIV. However, when entecavir is used to treat HBV in patients with HBV/HIV coinfection who are not on ART, the drug may select for the M184V

mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in patients with HBV/HIV coinfection, entecavir must be used in addition to a fully suppressive ARV regimen **(AII)**.[9]

- When 3TC is the only active drug used to treat chronic HBV in patients with HBV/HIV coinfection, 3TC-resistant HBV emerges in approximately 40% and 90% of patients after 2 and 4 years on 3TC, respectively. Therefore, 3TC or FTC, which is similar to 3TC, should be used in combination with other anti-HBV drugs **(AII)**.[10]
- In patients with HBV/HIV coinfection, immune reconstitution following initiation of treatment for HIV, HBV, or both can be associated with elevated transaminase levels, possibly because HBV-induced liver damage is primarily an immune-mediated disease.[11]
- Some ARV agents can increase transaminase levels. The rate and magnitude of these increases are higher with HBV/HIV coinfection than with HIV monoinfection.[12-14] The etiology and consequences of these changes in liver function tests are unclear because the changes may resolve with continued ART. Nevertheless, some experts suspend the suspected agent(s) when the serum alanine transferase (ALT) level increases to 5 to 10 times the upper limit of normal or at a lower threshold if the patient has symptoms of hepatitis. However, increased transaminase levels in persons with HBV/HIV coinfection may indicate hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution; thus, the cause of the elevations should be investigated before discontinuing medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe, as well as HBV DNA levels.

Recommendations for Patients with HBV/HIV Coinfection

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see Hepatitis B Virus Infection in the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents). Patients with chronic HBV should also be tested for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and, if nonimmune, receive the HAV vaccination. In addition, patients with chronic HBV should be advised to abstain from alcohol and counseled on prevention methods that protect against both HBV and HIV transmission.[15]
- Before ART is initiated, all persons who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication **(AIII)**, and the test should be repeated every 3 to 6 months to ensure effective HBV suppression. The goal of HBV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) is to prevent liver disease complications by sustained suppression of HBV replication.
- Since HBV reactivation has been observed in persons with HBV infection during interferon-free HCV treatment,[16,17] persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes agents with anti-HBV activity (such as [TDF or TAF] plus [FTC or 3TC]) prior to initiating HCV therapy **(AIII)**. The diagnosis of HBV reactivation should be considered in persons with current HBV infection who experience elevated liver enzymes during or immediately after HCV therapy.

Antiretroviral Drugs with Dual Activities against HBV and HIV

Among the ARV drugs, 3TC, FTC, TAF, and TDF all have activity against HBV. Entecavir is an HBV nucleoside analog which also has weak HIV activity. TAF is a tenofovir prodrug with HBV activity and potentially less renal and bone toxicities than TDF.

The efficacy of TDF versus TAF in patients with HBV monoinfection was evaluated in a randomized controlled trial of HBV treatment-naive and treatment-experienced HBeAg-negative patients. In this study,

TAF was noninferior to TDF based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = .47$).[18] TAF was also noninferior to TDF in HBeAg-positive patients with chronic HBV monoinfection with a similar percentage of patients achieving HBV DNA levels <29 IU/mL at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = .25$).[19] In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to 48 weeks also favored TAF.[18,19]

In patients with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy

The combination of (TAF or TDF) plus (3TC or FTC) should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection **(AII)**.[20-22] The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and for acceleration of bone loss. In a switch study in patients with HBV/HIV coinfection, study participants who switched from a primarily TDF-based ART regimen to the fixed-dose combination elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/c/TAF/FTC) maintained or achieved HBV suppression, with improved eGFR and bone turnover markers.[23] TAF/FTC-containing regimens currently approved for the treatment of HIV infection are not recommended for use in patients with creatinine clearance (CrCl) <30 mL/min. While data on switching from a TDF-based to a TAF-based ART regimen are limited, the data from the EVG/c/TAF/FTC switch study suggest that patients with HBV/HIV coinfection can switch to TAF/FTC-containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy

If TDF or TAF cannot safely be used, entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; however, entecavir should not be considered as part of the ARV regimen (BII).[24] Because entecavir and 3TC share a partially overlapping pathway to HBV resistance, it is unknown whether the combination of entecavir plus 3TC or FTC will provide greater virologic or clinical benefit than entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (approximately every 3 months) of the HBV DNA level to detect viral breakthrough.

Peginterferon alfa monotherapy for up to 48 weeks may also be considered in some patients with HBV/HIV coinfection. However, data on the use of this therapy in persons with HBV/HIV coinfection are limited and, given safety concerns, peginterferon alfa should not be used in persons with HBV/HIV coinfection who have decompensated cirrhosis.

HBV Drugs Not Recommended

Other HBV treatment regimens include telbivudine used in addition to a fully suppressive ARV regimen, or adefovir used in combination with 3TC or FTC and a fully suppressive ARV regimen.[20,25,26] However, data on these regimens in persons with HBV/HIV coinfection are limited. In addition, these regimens are associated with higher rates of HBV treatment failure and a higher incidence of toxicity when compared to regimens containing TDF, TAF, or entecavir. These toxicities include increased risk of renal disease with adefovir-containing regimens and increased risk of myopathy and neuropathy with telbivudine-containing regimens. Therefore, the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents **does not currently recommend** adefovir or telbivudine for patients with HBV/HIV coinfection.

Changing Antiretroviral Therapy

- **Need to discontinue ARV medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve such as those with compensated or decompensated cirrhosis.[8] These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.
- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other ARV agents that effectively suppress HIV **(AIII)**.

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Hepatitis C Virus/HIV Coinfection (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- All people with HIV should be screened for hepatitis C virus (HCV) infection **(AIII)**. Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII)**.
- Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most persons with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count **(AI)**.
- Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug-drug interactions and overlapping toxicities **(AIII)** (see discussion in the text below and in Table 13).
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes having their liver fibrosis stage assessed to inform the length of their therapy and subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII)**.
- Persons with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or IgG). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during HCV treatment with direct-acting antivirals (DAAs). Accordingly, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The treatment of hepatitis C virus (HCV) infection is rapidly evolving. Patients with HCV/HIV coinfection treated with all-oral, direct-acting antiviral (DAA) HCV regimens can achieve sustained virologic response (HCV cure) at rates comparable to those of patients with HCV mono-infection.[1-3] This section of the guidelines focuses on hepatic safety and drug-drug interaction issues related to HCV/HIV coinfection and the concomitant use of antiretroviral (ARV) agents and HCV drugs. For specific guidance on HCV treatment, clinicians should refer to the HCV Guidance from the American Association for the Study of Liver Diseases.

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of <20 years.[4,5] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[6-9] A meta-analysis found that patients with HCV/HIV coinfection had a three-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV monoinfection.[8] The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV coinfection, several studies have demonstrated that the rate of disease progression continues to exceed that observed in patients without HIV infection.[10,11] Whether HCV infection accelerates HIV progression, as measured by the occurrence of AIDS-related opportunistic infections (OIs) or death,[12] is unclear. With older ARV drugs, persons with chronic HCV co-infection experienced higher rates of hepatotoxicity than those seen in persons without HCV.[13,14] These higher rates have not been observed with the newer ARV agents that are currently in use.

Assessment of HCV/HIV Coinfection

- All patients with HIV should be screened for HCV infection using sensitive immunoassays licensed for

the detection of antibodies to HCV in blood.[15] At-risk HCV-seronegative patients should undergo repeat testing annually or as clinically indicated. HCV-seropositive patients should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection. Patients who test HCV RNA positive should undergo HCV genotyping and liver disease staging as recommended by the HCV Guidance.

- Patients with HCV/HIV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others.
- People with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or IgG).
  - Persons with evidence of active HBV infection (as determined by the presence of HBsAg) should be further evaluated and treated with ART that includes agents with anti-HIV and anti-HBV activities **(AIII)**.
  - Those who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination.
- Patients with HCV/HIV coinfection who are susceptible to hepatitis A virus (HAV) should be vaccinated.
- All patients with HCV/HIV coinfection are candidates for curative HCV treatment.

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

Initiation of ART for persons with HCV/HIV coinfection should follow the recommendations for all persons with HIV infection, taking into account the need for concurrent HCV treatment with oral DAA regimens, drug-drug interaction potentials, and the individual's HBV status.

Considerations When Starting Antiretroviral Therapy

The same regimens that are recommended for initial treatment of HIV in most ART-naive persons are also recommended for persons with HCV/HIV coinfection. Special considerations for ARV selection in persons with HCV/HIV coinfection include the following:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions with the HCV treatment regimen (see Table 13).
- In persons with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) prior to initiating HCV therapy **(AIII)**.
- Cirrhotic patients should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 8).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in patients with HCV/HIV coinfection than in those with HIV mono-infection. Individuals with HCV/HIV coinfection

who have advanced liver disease (e.g., cirrhosis, end-stage liver disease) are at greatest risk for DILI.[18] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[19] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and more often if clinically indicated. Mild to moderate fluctuations in ALT and/or AST levels (<5 times upper limit of normal [ULN]) are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART, but do warrant monitoring to ensure a return to baseline. Patients with significant elevations in ALT and/or AST levels (>5 times ULN), concomitant increase in total bilirubin, and/or concomitant symptoms (weakness, nausea, vomiting) should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis). If these signs and symptoms do not resolve, ART should be discontinued.

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug-drug interactions when used in combination. Prior to starting HCV therapy, the ART regimen may need to be modified to reduce the drug-drug interaction potential. Table 13 below provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients receiving ART that has been modified to accommodate HCV treatment, HIV RNA should be measured within 2 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. Clinicians should wait at least 2 weeks after ART modification before initiating an HCV DAA regimen. Clinicians should also wait for at least 2 weeks before resuming the original ART regimen after a patient completes the HCV DAA regimen. The prolonged half-life of some HIV and HCV drugs poses a potential risk of drug-drug interactions if a regimen is resumed soon after ART modification or HCV treatment completion.

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 1 of 4)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV DAA drugs are based on available PK interaction data or are predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data to make any recommendations, and these instances are indicated in the table. In all cases where HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and the HCV Guidance for updated information.

Note: Interactions with FPV, IDV, NFV, and SQV are **not** included in this table. Please refer to the FDA product labels for information regarding drug interactions with these HIV PIs.

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
NRTIs									
3TC	✓	✓	✓	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity.	✓ Monitor for TDF toxicity.	✓ Monitor for TDF toxicity.	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓	✓	✓	✓
PIs									
Unboosted ATV	✓	✓	✓	✓	✗	✗	✗	✓[b]	✗

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 2 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
PIs, continued									
ATV/r or ATV/c	✓ ↓ DCV dose to 30 mg/day	✓	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities.[d]	✓ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If coadministration is necessary, monitor for TDF-associated toxicities.[d]	✘	✘	✘	✓[c]	✘
DRV/r or DRV/c	✓	✓			✓ If a PI/r is used with TDF, ↑ TDF concentrations. Monitor for TDF-associated toxicities.[d] Consider monitoring for hepatotoxicity.[e]	✘	✘	✘	✘
LPV/r	✓	✓			✘	✘	✘	✘	✘
TPV/r	?	✘	✘	✘	✘	✘	✘	✘	✘
NNRTIs									
DOR	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓	✓	✓	✓
EFV	✓ ↑ DCV dose to 90 mg/day	✓		✘	✘	✘	✘	✘	✘
ETR	✓ ↑ DCV dose to 90 mg/day	✓		✘	✘	✘	✘	✘	✘

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 3 of 4)

Selected HIV Drugs	HCV Direct-Acting Antiviral Agents								
			Coformulated						
					SHOULD NOT BE USED IN THOSE WITH MODERATE TO SEVERE HEPATIC IMPAIRMENT (Cirrhosis classified as Child-Pugh class B or C)				
	NS5A Inhibitor	NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor	NS5A/NS5B Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor	NS5A Inhibitor/ NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[a]	Simeprevir
NNRTIs, continued									
NVP	✓ ↑ DCV dose to 90 mg/day	✓	✓ If used with TDF, monitor for TDF toxicity.	✘	✘	✘	✘	✘	✘
RPV	✓	✓		✓	✓	✓	✓	✘	✓
INSTIs									
BIC/TAF/FTC	✓	✓	✓	✓	✓	✓	✓	✓	✓
DTG	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓	✓	✓	✓
EVG/c/TDF/ FTC	✓ ↓ DCV dose to 30 mg/day	✓	✘	✓ If used with TDF, monitor for TDF toxicity.	✓ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[e]	✓ If used with TDF, monitor for TDF toxicity. Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
EVG/c/TAF/ FTC	✓ ↓ DCV dose to 30 mg/day	✓	✓	✓	✓ Consider monitoring for hepatotoxicity.[e]	✓ Consider monitoring for hepatotoxicity.[f]	✘	✘	✘
RAL	✓	✓	✓	✓	✓	✓	✓	✓	✓
CCR5 Antagonist									
MVC	✓	✓	✓	✓	✓	✓	✓	✘	✓

Table 13. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 4 of 4)

[a] Dasabuvir must be prescribed with ombitasvir/paritaprevir/RTV.

[b] Reduce ATV dose to 300 mg and instruct the patient to take it in the morning at same time as ombitasvir/paritaprevir/RTV plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.

[c] This HCV regimen contains RTV. If ATV is part of the ARV regimen, prescribe ATV 300 mg without COBI or RTV. It should be taken in the morning at the same time as ombitasvir/paritaprevir/RTV plus dasabuvir. Resume RTV or COBI regimen when HCV therapy is completed.

[d] Consider using an alternative HCV treatment or ARV regimen to avoid increases in TDF exposure. If co-administration is necessary, monitor patient for TDF-associated adverse reactions.

[e] Voxilaprevir exposures can increase when it is coadministered with pharmacologically boosted DRV or EVG. Until more safety data in clinical settings becomes available, patients who are receiving voxilaprevir and pharmacologically boosted DRV or EVG should be monitored for hepatotoxicity.

[f] Glecaprevir exposures can increase when it is coadministered with EVG/c. Until more safety data in clinical settings becomes available, patients who are receiving glecaprevir and EVG/c should be monitored for hepatotoxicity.

Key to Symbols:

✓ = ARV agents that can be used concomitantly

✘ = ARV agents not recommended

? = data limited or not available on pharmacokinetic interactions with ARV drug

↑ = increase

↓ = decrease

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = Food and Drug Administration; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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Panel's Recommendations

- Selection of a tuberculosis (TB)-preventive treatment for individuals living with HIV and coinfected with latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:
  - Any ART regimen can be used when isoniazid alone is used for LTBI treatment **(AII)**.
  - Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine **(AIII)**.
  - If rifampin or rifabutin is used to treat LTBI, clinicians should review Tables 19a through 19e to assess the potential for interactions among different antiretroviral (ARV) drugs and the rifamycins **(BIII)**.
- All patients with both HIV and active TB who are not on ART should be started on ART as described below:
  - **In patients with CD4 counts <50 cells/mm³:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.
  - **In patients with CD4 counts ≥50 cells/mm³:** Initiate ART within 8 weeks of starting TB treatment **(AIII)**.
  - **In all pregnant women with HIV:** Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV **(AIII)**.
  - **In patients with tuberculous meningitis:** Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial **(AI)**.
- Rifamycins are critical components of TB treatment regimens and should be included for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycins have a considerable potential for drug-drug interactions. Clinicians should review Tables 19a through 19e to assess the potential for interactions among different ARV drugs and the rifamycins **(BIII)**.

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*

Management of Latent Tuberculosis Infection in HIV-Infected Patients

According to the World Health Organization (WHO), approximately one-third of the world's population is infected with tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.[1] People with HIV who are coinfected with TB have a much higher risk of developing active TB than individuals who do not have HIV, and this risk increases as immune deficiency worsens.[2]

Anti-Tuberculosis Therapy as Preventive Tuberculosis Treatment

Many clinical trials have demonstrated that treatment for latent tuberculosis infection (LTBI) reduces risk of active TB in people with HIV, especially those with a positive tuberculin skin test.[3] After active TB disease has been excluded, the Centers for Disease Control and Prevention (CDC) recommends one of the following regimens for LTBI treatment (http://www.cdc.gov/tb/topic/treatment/ltbi.htm):

- Isoniazid (INH) daily or twice weekly for 9 months
- INH plus rifapentine once weekly for 12 weeks
- Rifampin (or rifabutin) daily for 4 months

For more than 30 years, INH has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadminstered with any antiretroviral (ARV) regimen and is safe to use in pregnant women. The combination of INH and rifapentine administered weekly for 12 weeks as directly observed therapy (DOT) is another treatment option for LTBI. In the PREVENT TB study, rifapentine plus INH for 12 weeks was as safe and effective as 9 months of INH alone in preventing TB in patients with HIV who were not on ART.[4] There was no difference in TB incidence in 1,148 South African adults with HIV who were randomized to receive rifapentine plus INH weekly for 12 weeks, rifampin plus INH twice weekly for 12 weeks, INH daily for 6 months, or continuous INH therapy.[5] Although rifapentine induces cytochrome P (CYP) 450 isoenzymes and

can potentially cause significant drug-drug interactions, there are now pharmacokinetic (PK) data supporting its use with efavirenz (EFV)[6] and raltegravir (RAL)[7] **(AIII)**. Rifampin or rifabutin for 4 months may also be considered for LTBI treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 19a through 19c).

If a patient with HIV is a contact of an individual with drug-resistant TB, the options for LTBI treatment should be modified. In this setting, consultation with a TB expert is advised.

Antiretroviral Therapy's Effect in Preventing Active Tuberculosis

Accumulating evidence also suggests that ART can prevent active TB. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV who did not meet WHO criteria for ART initiation to one of four study arms: deferred ART (until WHO criteria were met); deferred ART plus INH preventive therapy (IPT); early ART; or early ART plus IPT.[8] Among participants with CD4 T lymphocyte (CD4) counts >500 cells/mm^3, starting ART immediately reduced the risk of death and serious HIV-related illness, including TB, by 44% (2.8 vs. 4.9 severe events per 100 person-years with immediate and deferred ART, respectively; $P = .0002$). Six months of IPT independently reduced the risk of severe HIV morbidity by 35% (3.0 vs. 4.7 severe events per 100 person years with IPT and no IPT, respectively; $P = .005$) with no overall increased risk of other adverse events. In the START study, 4,685 participants with CD4 counts >500 cells/mm^3 were randomized to receive immediate ART or ART deferred until their CD4 count dropped to 350 cells/mm^3 or until they developed a clinical condition that required ART. TB was one of the three most common clinical events, occurring in 14% of participants in the immediate initiation group and 20% of participants in the deferred initiation group.[9] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with high prevalence of HIV/TB coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in patients with HIV should follow the general principles guiding treatment for individuals without HIV. The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (Adult and Adolescent OI Guidelines)[10] include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include:

- When to start ART;
- Significant PK drug-drug interactions between anti-TB and ARV agents;
- The additive toxicities associated with concomitant ARV and anti-TB drug use; and
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Tuberculosis Diagnosed While Patient is Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the ARV regimen should be assessed with particular attention to potential PK interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 19a through 19c for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

In patients not taking ART at the time of TB diagnosis, delaying ART initiation for an extended period may

result in further immune decline with increased risk of new opportunistic diseases and death, especially in patients with advanced HIV disease. Several randomized controlled trials have attempted to address the optimal timing of ART initiation in the setting of active TB disease. The results of these trials have caused a paradigm shift favoring earlier ART initiation in patients with TB. The timing of ART in specific patient populations is discussed below.

Patients with CD4 count <50 cells/mm³: Three large randomized clinical trials in patients with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm³ significantly reduced AIDS events or deaths.[11-14] In these studies, early ART was defined as starting ART within 2 weeks and at no later than 4 weeks after initiation of TB therapy. In all three studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm³ **(AI)**.

Patients with CD4 counts ≥50 cells/mm³: In the three studies mentioned above, there was no survival benefit for patients with CD4 count ≥50 cells/mm³ who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality in the SAPiT-1 study.[11] Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in patients with TB and CD4 counts over 50 cells/mm³. However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the the Panel recommends ART initiation within 8 weeks of starting TB treatment for those with ≥50 cells/mm³ **(AIII)**.

Patients with drug-resistant TB: Mortality rates in patients with multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB and HIV are very high.[15] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients,[16,17] but the optimal timing for initiation of ART is unknown. Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(BIII)**.

Patients with TB meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, patients were randomized to immediate ART or to ART deferred 2 months after initiation of TB treatment. A significantly higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those with deferred therapy (80.3% vs. 69.1% for early and deferred ART, respectively; $P = 0.04$).[18] Therefore, caution should be exercised when initiating ART early in patients with TB meningitis **(AI)**.

Pregnant patients: All pregnant women with HIV and active TB should be started on ART as early as feasible, both for treatment of maternal HIV infection and to prevent perinatal transmission of HIV **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and should take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).[19]

Drug Interaction Considerations

Rifamycins are a crucial component of TB treatment regimens. However, they are associated with a considerable potential for PK drug interactions. Rifampin is a potent inducer of the hepatic CYP 450 (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes. Rifabutin and rifapentine are CYP 3A4 substrates and inducers. As potent enzyme inducers, the rifamycins can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected by CYP induction include all protease inhibitors (PIs), non-nucleoside reverse

transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs) elvitegravir (EVG) and the CCR5 antagonist maraviroc (MVC). Additionally, UGT1A1 induction may hasten the metabolism of the INSTIs dolutegravir (DTG) and RAL. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and the fusion inhibitor enfuvirtide are not expected to have significant drug interactions with the rifamycins. As a P-gp substrate, tenofovir alafenamide (TAF)'s drug exposure may be reduced by rifamycins; therefore, concomitant administration of TAF and a rifamycin is not recommended at this time.[20] Tables 19a through 19c outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly.

As a potent enzyme inducer, rifampin use leads to significant reduction in ARV drug exposure; therefore, use of rifampin is not recommended for patients receiving PIs (boosted or unboosted), EVG, etravirine (ETR), rilpivirine (RPV), or TAF. Increased ARV doses are needed when rifampin is used with DTG, RAL, or MVC. In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.[21,22] Several observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of EFV.[23,24] Even though the current EFV label recommends increasing the EFV dose from 600 mg to 800 mg once daily in patients weighing >50 kg,[25] this dosage increase is generally not necessary.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 19a through 19c for dosing recommendations).

Rifapentine is a long-acting rifamycin which can be given once weekly with INH to treat latent TB infection.[26] Once-daily rifapentine is a more potent inducer than daily rifampin therapy.[27] The impact of once weekly dosing of rifapentine on the PKs of most ARV drugs has not been systematically explored. Once-daily rifapentine did not affect the oral clearance of EFV in individuals with HIV[28] and has minimal impact on EFV exposure when given once weekly,[6] whereas once-weekly rifapentine led to increase instead of decrease in RAL drug exposure in healthy volunteers.[7] Pending additional PK data on the effect of rifapentine on other ARV drugs, once-weekly INH plus rifapentine for LTBI treatment should only be given to patients receiving either an EFV- or RAL- based regimen **(AIII)**.

After selecting the ARV drugs and rifamycin to use, clinicians should determine the appropriate dose of each, and should closely monitor the patients to assure good control of both TB and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, adequacy of drug exposure (consider therapeutic drug monitoring [TDM]), or presence of acquired HIV or TB drug resistance.

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). TB-associated IRIS (TB-IRIS) has been reported in 8% to more than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[29,30] Predictors of IRIS include a baseline CD4 count <50 cells/mm^3; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and a less than 30-day interval between initiation of TB and HIV treatments.[24,31-33] Most IRIS in HIV/TB disease occurs within 3 months of the start of ART.

Manifestations of unmasking TB-IRIS are characterized by their marked inflammatory nature, such as high fever, respiratory distress, lymphadenitis, abscesses, and sepsis syndrome. Manifestations of paradoxical TB-

IRIS include fevers, new or worsening lymphadenopathy, new or worsening pulmonary infiltrates, enlarging pleural effusions, and new or enlarging tuberculomas.

IRIS ranges from mild to severe to life-threatening. Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids, although data on the optimal dose, duration of therapy, and overall safety and efficacy are limited.[34] In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

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Limitations to Treatment Safety and Efficacy

Adherence to the Continuum of Care (Last reviewed October 17, 2017)

Key Summary of Adherence to the Continuum of Care

- Linkage-to-care and adherence to both antiretroviral therapy (ART) and clinic appointments should be regularly assessed.
- An individual's barriers to adherence to ART and appointments should be assessed before initiation of ART and regularly thereafter.
- Patients with ART adherence problems should be placed on regimens with high genetic barriers to resistance, such as dolutegravir (DTG) or boosted darunavir (DRV). Side effects, out-of-pocket costs, convenience, and patient preferences also need to be considered.
- Patients having difficulties with adherence to appointments or ART should be approached in a constructive, collaborative, nonjudgmental, and problem-solving manner.
- The approach to improved adherence should be tailored to each person's needs (or barriers to care). Approaches could include, but are not limited to:
  - Changing ART to simplify dosing or reduce side effects
  - Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments
  - Allowing flexible appointment scheduling
  - Assisting with transportation, or
  - Linking patients to counseling to overcome stigma, substance use, or depression.
- Multidisciplinary approaches to find solutions to ART and appointment adherence problems are often necessary, including collaboration with social work and case management (to the extent available). The clinician's role is to help the patient understand the importance of adherence to the continuum of care and reveal barriers to adherence, and link the patient to resources to overcome those barriers.
- A summary of best practice interventions to improve linkage, retention, and adherence can be found at a Centers for Disease Control and Prevention compendium (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

Introduction

Treatment adherence includes initiating care with an HIV provider (linkage to care), regularly attending appointments (retention in care), and adherence to antiretroviral therapy (ART). The concept of a "continuum of care" has been used to describe the process of HIV testing, linkage to HIV care, initiation of ART, adherence to treatment, retention in care, and virologic suppression.[1-3] The U.S. Centers for Disease Control and Prevention (CDC) estimates that HIV has not yet been diagnosed in about 13% of the people living with HIV in the United States. After receiving an HIV diagnosis, about 75% of individuals are linked to care within 30 days. However, only 57% of persons who receive an HIV diagnosis are retained in HIV care. It is estimated that only approximately 55% of persons with diagnosed HIV are virally suppressed because of poor linkage to care and retention in care.[4] The data for adolescents and young adults are even more sobering: only 51% of youth living with HIV receive a diagnosis, 68% are linked to care within 1 month, and 55% are retained in care. As a result, adolescents and young adults had the lowest rate of viral suppression among all age groups, at only 44%.[5] Outcomes along the continuum also vary by geographic region and other population characteristics, such as sex, race/ethnicity, and HIV risk factors.[4] To achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, adherence to each step in the continuum of care is critical.[6] It is also important to realize that retention and adherence are not static states. Life events, changes in insurance status, comorbid conditions and health system changes can cause people to shift back and forth on the continuum. Knowledgeable providers and high-quality system processes are vital in promoting rapid linkage and sustained retention in care and adherence to ART.

This section provides guidance on linking patients to care, assessing and improving retention in care, and assessing and improving adherence to ART. The CDC maintains a compendium of evidence-based

and evidence-informed interventions to improve linkage, retention, and adherence (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html). In addition, a number of other groups and organizations have provided guidance for improving adherence to the steps in the care continuum.[6,7]

Linkage to Care

Receiving a diagnosis of HIV infection can be traumatic and linkage to care efforts must be delivered with sensitivity and persistence. The time from diagnosis to linkage to care can be affected by many factors, including insufficient socioeconomic resources, active substance use, mental health problems, stigma, and disease severity (symptomatic HIV is associated with more successful linkage).[8-12] In the United States, youth, people who use injection drugs, and black/African American persons have lower rates of linkage to care.[4] Some health system-associated factors have also been associated with linkage success or failure. Co-location of testing and treatment services[11] and active linkage services (e.g., assisting the patient in setting up appointments, maintaining an active relationship with the patient until linkage is completed, and providing linkage case management services)[13-15] bolster linkage to care. Conversely, passive linkage (e.g., only providing names and contact information for treatment centers) is associated with lower linkage to care.

Monitoring Linkage to Care

Linking to HIV care after a new diagnosis of HIV infection is defined as completing an outpatient appointment with a clinical provider who has the skills and ability to treat HIV infection, including prescribing ART. Patients should be linked to care as soon as possible after diagnosis with HIV, preferably within 30 days. Monitoring linkage is a critical responsibility so that interventions can effectively reach persons who are not linked to care. If the facilities that diagnose and treat an individual are the same or share the same electronic medical record system, it is relatively straightforward to monitor linkage to care. Monitoring linkage for persons whose HIV is diagnosed outside the treatment provider's healthcare system is difficult and generally is the responsibility of the diagnosing provider/entity and the public health authority. However, once a patient makes contact with the treating clinical system, he or she should be engaged in linkage efforts and monitored for successful linkage to and retention in HIV care.

Improving Linkage to Care

Strategies to improve linkage to care are summarized in Table 14. Linkage efforts should include immediate referral to care at diagnosis, appointment reminders, and outreach efforts if needed.[13] The only intervention shown to increase linkage to care in a randomized trial conducted in the United States is the Anti-Retroviral Treatment and Access to Services (ARTAS) intervention.[14] ARTAS is a strength-based intervention which aims to facilitate linkage to and retention in care for persons with recently diagnosed HIV. The ARTAS intervention was tested in four cities and enrolled a diverse group of persons. The participants in the ARTAS intervention trial were randomized to either an intervention arm or a control arm. Participants randomized to the control arm received information about HIV and care resources and a referral to a local *HIV Medical* provider. Each participant in the intervention arm worked with an ARTAS interventionist for five sessions, 90 days, or until linkage—whichever came first. The interventionist helped the participant to identify and use his or her strengths, abilities, and skills to link to HIV care, and linked the participant to community resources. Linkage to care, defined as completing at least one visit with an HIV clinician within the first 6 months, was greater among the ARTAS participants than the control participants (78% vs. 60%, adjusted RR = 1.36, $P < 0.001$). Furthermore, a greater percentage of ARTAS participants were retained in care, defined as visiting an HIV clinician at least once in each of the first two 6-month blocks after enrollment (64% vs. 49% for ARTAS and control participants, respectively; adjusted RR = 1.41, $P = 0.006$). ARTAS has been replicated in a community-based study.[15] CDC supports free training in the ARTAS intervention (https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/PublicHealthStrategies/ARTAS.aspx). Other studies support the importance of post-test counseling to educate, motivate, and present positive messages about

living with HIV,[16] peer support,[17] and engaging with the patient at the clinic in advance of the visit with the provider.[18] Financial incentives did not increase linkage to care within 90 days in a large randomized trial.[19]

Retention in Care

Poor retention in HIV care is associated with greater risk of death.[20,21] Poor retention is more common in persons who are substance users, have serious mental health problems, have unmet socioeconomic needs (e.g., housing, food, or transportation), lack financial resources or health insurance, have schedules that complicate adherence, have been recently incarcerated, or face stigma.[22-25] At the provider and health system level, low trust in providers and a poor patient-provider relationship have been associated with lower retention, as has lower satisfaction with the clinic experience.[26-28] Availability of appointments and timeliness of appointments (i.e., long delay from the request for an appointment to the appointment's date) and scheduling convenience are also factors.

Monitoring Retention in Care

Retention in care should be routinely monitored.[6] There are various ways to measure retention, including measures based on attended visits over a defined period of time (constancy measures), and measures based on missed visits.[29] Both approaches are valid and independently predict survival.[30] Missed visits and a prolonged time since last visit are relatively easy to measure and should trigger efforts to retain or re-engage a person in care. Constancy measures (e.g., at least two visits that are at least 90 days apart over 1 year, or at least one visit every 6 months over the last 2 years), can be used as clinic quality assurance measures.

Improving Retention in Care

Strategies to improve retention in care are summarized in Table 14. The Retention through Enhanced Personal Contact (REPC) intervention was tested in a randomized trial in six clinics in the United States. The intervention relied on personal contact by an interventionist with at-risk patients. It included a brief face-to-face meeting upon returning to care and at each clinic visit and three types of phone calls: to check on patients between visits, as appointment reminders just before visits, and to attempt to reschedule missed visits. REPC resulted in small but significant improvements in retention in care, including in racial/ethnic minority populations and persons with detectable plasma HIV RNA.[31] In-clinic opioid replacement therapy helps opioid users remain in care.[32] An intervention using the electronic medical record to alert providers when patients had suboptimal follow-up or high viral loads also improved retention in care.[33] On the other hand, in two randomized trials involving out-of-care, hospitalized patients with HIV, peer counselors and patient navigators did not improve relinkage to care after hospital discharge.[34,35] Data from nonrandomized studies support:

- Clinic-wide marketing (e.g., posters, brochures, and customer service training of patient-facing staff) to promote attending scheduled visits and provide patients a welcoming and courteous experience,[36]
- Stepped case management and social and outreach services,[37] and
- "Data to Care" approaches which use clinic and public health data to reach out-of-care persons and re-engage them into care (see https://effectiveinterventions.cdc.gov/en/highimpactprevention/publichealthstrategies/DatatoCare.aspx).[38-40] However, the effectiveness of "data to care" interventions is variable and privacy concerns must be adequately addressed.

Overall, these data support the concept that all clinic personnel, from the facilities staff to nurses to providers, play important roles in supporting retention in care by providing the optimal patient care experience, constructively affirming attendance rather than criticizing non-attendance, and collaboratively problem solving with patients to overcome barriers to care.[27,31,36] Flexible appointment schedules, expanded clinic hours, and copay and other financial or insurance assistance such as that provided by the Ryan White program will also provide patients with uninterrupted access to clinical care. Guidelines regarding linkage

and retention have been published.[6,7] CDC maintains a compendium of evidence-based and evidence-informed interventions (https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html).

The use of financial incentives or rewards to promote retention in care has been studied. A large study randomized clinic sites to financial incentives or standard-of-care. At baseline, 45% of the patients were retained in care in these clinics. The relative increase in the proportion of participants retained in care was 9% higher in clinics offering incentives than in standard-of-care clinics. Viral suppression also improved 4% at financial incentive clinics, from a baseline of 62%.[19] In another large, randomized study of persons out-of-care and hospitalized, financial incentives plus patient navigation did not lead to sustained improvement in retention or viral load suppression over that achieved with standard care.[34] The use of financial incentives therefore remains experimental and cannot be recommended for routine care at this time.

Adherence to Antiretroviral Therapy

Adherence to ART can be influenced by a number of factors, including the patient's social situation and clinical condition, the prescribed regimen, and the patient-provider relationship.[41] Poor adherence is often a consequence of one or more behavioral, structural, and psychosocial barriers (e.g., depression and other mental illnesses, neurocognitive impairment, low health literacy, low levels of social support, stressful life events, busy or unstructured daily routines, active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications due to financial and insurance status).[42-44]

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens,[45] including those with low pill burden (even if not one pill once daily), without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[46,47] Single-tablet regimens (STR) that include all antiretrovirals in one pill taken once daily are easier for people to use. However, data to support or refute the superiority of a STR versus a once-daily multi-tablet regimen (MTR), as might be required for the use of some soon-to-be-available generic-based antiretroviral (ARV) regimens, are limited. There are demonstrated beneficial effects on virologic suppression in switch studies, in which persons on MTR are randomized to stay on MTR or switch to STR.[48] Whether an STR is beneficial in treatment-naive patients is not known, with at least one large observational cohort study showing benefit of once-daily STR versus once-daily MTR, but only when switches for simplification of MTR were considered failures.[47,49] Comparisons of these regimens are hampered since not all drugs and classes are available as STR.

Characteristics of the clinical setting can also have important structural influences on the success or failure of medication adherence. Settings that provide comprehensive multidisciplinary care (e.g., by case managers, pharmacists, social workers, and mental health and substance abuse providers) support patients' complex needs, including their medication adherence-related needs. Drug abuse treatment programs are often best suited to address substance use and may offer services that promote adherence, such as directly observed therapy (DOT).

Monitoring Adherence to Antiretroviral Therapy

Adherence to ART should be assessed and addressed in a constructive and nonjudgmental manner at every visit. Given the potency of contemporary ART, a detectable viral load identified during chronic care for a patient with stable access to ART is most likely the result of poor adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool. Carefully assessed patient self-report of high-level adherence to ART has been associated with favorable viral load responses.[50,51] Patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self-report often depends on how the clinician elicits the information. It is most reliable when ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses. To allow patients to disclose lapses in adherence, some experts suggest inquiring about the number of missed doses during a defined time period. For example, for a patient with a

detectable viral load, a provider might state, "I know it is difficult to take medicine every day. Most people miss doses at least sometimes. Thinking about the last 2 weeks, how many times have you missed doses? Please give me a rough estimate so I can help you take the best care of yourself." Other research supports simply asking patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale.[52,53]

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source. Because pill counts can be altered by patients, are labor intensive, and can be perceived as confrontational, they are generally not used in routine care. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices (e.g., Medication Event Monitoring System [MEMS] bottle caps and dispensing systems). However, these methods are costly and are generally reserved for research settings.

Improving Adherence to Antiretroviral Therapy

Strategies to improve adherence to ART are summarized in Table 14. Just as they support retention in care, all health care team members play integral roles in successful ART adherence programs.[51,54-56] An increasing number of interventions have proven effective in improving adherence to ART (for descriptions of the interventions, see http://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html). The many options can be customized to suit a range of needs and settings.

It is important that each new patient receives and understands basic information about HIV infection, including the goals of therapy (achieving and maintaining viral suppression, which will decrease HIV-associated complications and prevent transmission), the prescribed regimen (including dosing schedule and potential side effects), the importance of adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. Patients must also be positively motivated to initiate therapy, which can be assessed by simply asking patients if they want to start treatment for HIV infection. Clinicians should assist patients in identifying facilitating factors and potential barriers to adherence, and develop multidisciplinary plans to attempt to overcome those barriers. Processes for obtaining medications and refills should be clearly described. Transportation to pharmacy and to clinic visits should be assessed with linkage to appropriate services as needed. Plans to ensure uninterrupted access to ART via insurance, copay assistance, pharmaceutical company assistance programs, or AIDS Drug Assistance Programs (ADAP), for example, should be made and reviewed with the patient. Much of this effort to inform, motivate, and reduce barriers can be achieved by support staff, and can be accomplished concomitant with, or even after, starting therapy.[57-60] While delaying the initiation of ART is rarely indicated, some patients may not be comfortable starting treatment. Patients expressing reluctance to initiate ART should be engaged in counseling to understand and overcome barriers to ART initiation. Although homelessness, substance use, and mental health problems are associated with poorer adherence, they are not predictive enough at the individual level to warrant withholding or delaying therapy given the simplicity, potency, and tolerability of contemporary ART. Rapid ART initiation at the time of HIV diagnosis has been pursued as a strategy to increase viral load suppression and retention in care, but safety data, data on intermediate or long-term outcomes, and data from randomized controlled trials conducted in high-resource settings are currently lacking.[57-60] For more details, see Initiation of Antiretroviral Therapy.

The first principle of successful treatment is to design a plan to which the patient can commit.[61,62] It is important to consider the patient's daily schedule; tolerance of pill number, size, and frequency; and any issues affecting absorption (e.g., use of acid-reducing therapy and food requirements). With the patient's input, a medication choice and administration schedule should be tailored to his or her daily activities. Clinicians should explain to patients that their first regimen is usually the best option for a simple regimen that affords long-term treatment success. Establishing a trusting patient-provider relationship and maintaining good communication will help to improve adherence and long-term outcomes. Medication taking can also be enhanced using medication reminder aids. There is strongest evidence for text messaging, but pill box monitors, pill boxes, and alarms may also improve adherence.[63-67]

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed viral load and increases in CD4 T lymphocyte cell counts. Motivational interviewing has also been used with some success.[68-70] Other effective interventions include nurse home visits, a five-session group intervention, and couples- or family-based interventions. Interventions involving several approaches are generally more successful than single-strategy interventions, and interventions based on cognitive behavioral therapy and supporter interventions have been shown to improve viral suppression.[71] Problem-solving approaches that vary in intensity and culturally tailored approaches also are promising.[70,72,73] To maintain high levels of adherence in some patients, it is important to provide substance abuse therapy and to strengthen social support. DOT has been effective in providing ART to active drug users[74] but not to patients in a general clinic population[75] or in home-based settings with partners responsible for DOT.[76] The use of incentives or rewards to promote adherence has been studied, and they have been shown to improve adherence in one study.[19] However, the durability and feasibility of financial incentives are not known at this time, hence rewards for adherence are not generally recommended.[34,77,78]

Conclusion

Even armed with accurate information about a patient's adherence and barriers to ART and appointment adherence, clinicians often fail to engage patients in a productive conversation and instead simply tell patients to be adherent and offer warnings about what might ensue with continued poor adherence. This approach fails to acknowledge a patient's barriers to adherence, fails to provide the patient with actionable information, erodes rather than builds the patient-provider relationship, and has been demonstrated to not improve adherence.[79,80] At the same time, however, many of the interventions shown to improve adherence are difficult to implement in routine care. Nonetheless, effective lessons from this body of research can be applied to routine care to improve linkage to care, adherence to ART, and adherence to appointments. These lessons include the following:

- Regularly assess adherence to ART and appointments.
- Engage a patient who is struggling with adherence at any step on the care continuum with a constructive, collaborative, nonjudgmental, and problem-solving approach rather than reprimanding them or lecturing them on the importance of adherence.
- Elicit an individual's barriers to adherence, which may include personal barriers (e.g., substance use, housing instability, stigma, lack of transportation), clinic barriers (e.g., limited clinic hours, processes that make it more difficult to obtain prescriptions or schedule appointments), and system barriers (e.g., copays, prior approvals, processes that complicate maintaining pharmacy benefits or obtaining refills).
- Tailor approaches to improve adherence to an individual's needs and barriers, for example, by changing ART to simplify dosing or reduce side effects, finding resources to assist with copays or other out-of-pocket costs (see Table 14) to maintain an uninterrupted supply of ART and access to clinicians, or linking patients to counseling to overcome stigma, substance use, or depression.
- Place patients with apparent ART adherence problems on regimens with high genetic barriers to resistance, such as dolutegravir or boosted-darunavir regimens. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and patient preferences since the only regimen that will work is the one the patient can obtain and is willing and able to take.
- Understand that multidisciplinary approaches and time to understand and address barriers are needed in many situations, and that the clinician's role is to help the patient to understand the importance of adherence to the continuum of care and reveal any barriers to adherence, and link the patient to resources to overcome those barriers.

Table 14. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 1 of 2)

Strategies	Examples
Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team.	• Care providers, nurses, social workers, case managers, pharmacists, and medication managers.
Strengthen early linkage to care and retention in care.	• Encourage health care team participation in linkage to and retention in care. • Use ARTAS training (if available).
Evaluate patient's knowledge about HIV infection, prevention, and treatment and, based on this assessment, provide HIV-related information.	• Keeping the patient's current knowledge base in mind, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, therapeutic and prevention consequences of poor adherence, and importance of staying in HIV care.
Identify facilitators, potential barriers to adherence, and necessary medication management skills both before starting ART and on an ongoing basis.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges, including depression, mental illnesses, levels of social support, levels of alcohol consumption and current substance use, nondisclosure of HIV serostatus, and stigma. • Identify and address language and literacy barriers. • Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of poor adherence). • Ask about medication-taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers). • Assess structural issues, including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications, transportation problems.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage (e.g., Common Patient Assistance Program Application (CPAPA): http://bit.ly/CommonPAPForm; Pharmaceutical Company HIV Patient Assistance Programs and Cost-Sharing Assistance Programs: http://bit.ly/1XlahyN • Provide resources about stable housing, social support, transportation assistance, and income and food security.
Involve the patient in ARV regimen selection.	• Review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of poor adherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based or DTG-based ART if poor adherence is anticipated. • Consider use of STR formulations. • Assess if cost/copayment for drugs will affect adherence and access to medications.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale or self-reported assessment. • Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white-coat adherence" responses. • Ensure that other members of the health care team also assess and support adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or nondetectable levels of HIV viral load and increases in CD4 cell counts. • Thank patients for attending their appointments.

Table 14. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 2 of 2)

Strategies	Examples
Identify the type of and reasons for poor adherence and target ways to improve adherence.	• Failure to understand dosing instructions. • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements, polypharmacy). • Pill aversion or pill fatigue. • Adverse effects. • Inadequate understanding of drug resistance and its relationship to adherence. • Patient is unaware of appointments or appointments are not scheduled with proper patient input. • Cost-related issues (copays for medications or visits, missed work time). • Depression, drug and alcohol use, homelessness, poverty. • Stigma of taking pills or attending HIV-related appointments. • Nondisclosure of status leading to missed doses, refills, or appointments.
Select from among available effective adherence and retention interventions.	• See https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html for a summary of best practice interventions to improve linkage, retention, and adherence. • Use adherence-related tools to complement education and counseling interventions (e.g., text messaging, pill box monitors, pill boxes, alarms). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates, transportation assistance). • Use patient prescription assistance programs (see above, under "Provide needed resources"). • Use motivational interviews. • Provide outreach for patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Recognize positive clinical outcomes resulting from better adherence. • Arrange for DOT in persons in substance use treatment (if feasible). • Enhance clinic support and structures to promote linkage and retention (reminder calls, flexible scheduling, open access, active referrals, and improved patient satisfaction).
Systematically monitor retention in care.	• Record and follow up on missed visits.

Key to Acronyms: ART = antiretroviral therapy; ARTAS = Anti-Retroviral Treatment and Access to Services; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DOT = directly observed therapy; DTG = dolutegravir; PI/r = ritonavir-boosted protease inhibitor; STR = single tablet regimen

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Adverse Effects of Antiretroviral Agents (Last updated October 25, 2018; last reviewed October 25, 2018)

Adverse effects have been reported with all ARV drugs and, in the earlier era of combination ART, adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence.[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, less than 10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated, because most clinical trials use highly specific inclusion criteria when enrolling participants and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes, accelerated vascular disease, kidney dysfunction, and bone loss. To achieve sustained viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and overcome. The clinician must consider potential adverse effects when selecting an ARV regimen, as well as the individual patient's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of or exacerbate adverse effects. For example, underlying liver disease from alcohol use, co-infection with viral hepatitis, and/or liver steatosis[2,3] may increase the risk of hepatotoxicity when drugs such as efavirenz (EFV) or protease inhibitors are used; psychiatric disorders may be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors;[4,5] and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications.
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[6,7] EFV neuropsychiatric toxicity and QTc prolongation,[8,9] and atazanavir (ATV)-associated hyperbilirubinemia.[10]

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. Table 15 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 1–6.