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

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

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (http://aidsinfo.nih.gov).

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**Resistance Testing**

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

**Co-Receptor Tropism Testing**

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

**Dolutegravir and Association with Neural Tube Defects**

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

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

**What to Start**

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

- **Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC):** BIC is a new INSTI that is approved by the Food and Drug Administration (FDA) as part of a single-tablet regimen (STR) that also includes TAF and FTC. This regimen is now classified as a Recommended Initial Regimen for Most People with HIV.

- **Elvitegravir/Cobicistat/Emtricitabine with Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate (EVG/c/FTC/TAF or EVG/c/FTC/TDF):** These regimens have been moved to the category of Recommended Initial Regimens in Certain Clinical Situations. This change was made because these combinations include cobicistat, a pharmaco-enhancer that inhibits cytochrome P450 3A4 and increases the likelihood of drug-drug interactions. EVG also has a lower barrier to resistance than DTG and BIC.

- **Doravirine (DOR):** DOR, a new non-nucleoside reverse transcriptase inhibitor, was recently approved by the FDA and is available as a single-drug tablet and as part of an STR that also includes TDF.
and lamivudine (3TC). DOR/TDF/3TC and DOR plus TAF/FTC have been added to the category of Recommended Initial Regimens in Certain Clinical Situations.

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

**Virologic Failure**

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

**Optimizing Antiretroviral Therapy in the Setting of Viral Suppression**

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

**Exposure-Response Relationship and Therapeutic Drug Monitoring Section**

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

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

• [Hepatitis C Virus/HIV Coinfection](#)
• [Adverse Effects of Antiretroviral Agents](#)
• [Monthly Average Prices of Commonly Used Antiretroviral Drugs](#)
• [Drug-Drug Interactions](#)
• [Appendix B Tables: Characteristics of Antiretroviral Drugs and Antiretroviral Dosing Recommendations in Patients with Renal and Hepatic Insufficiency](#)
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Key to Acronyms: C = Co-Chair; ES = Executive Secretary; M = Member; PI = Principal Investigator
Introduction (Last updated January 28, 2016; last reviewed January 28, 2016)

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition. In addition, ART is highly effective at preventing HIV transmission. However, only 55% of people with HIV in the United States have suppressed viral loads, mostly resulting from undiagnosed HIV infection and failure to link or retain diagnosed patients in care.

The Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARVs) used to treat adults and adolescents with HIV in the United States. The Panel reviews new evidence and updates recommendations when needed. These guidelines include recommendations on baseline laboratory evaluations, treatment goals, benefits of ART and considerations when initiating therapy, choice of the initial regimen for ART-naive patients, ARV drugs or combinations to avoid, management of treatment failure, management of adverse effects and drug interactions, and special ART-related considerations in specific patient populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children to provide recommendations for adolescents at different stages of growth and development. Recommendations for ART regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., sexual maturity rating [SMR] IV and V). Clinicians should follow recommendations in the Pediatric Guidelines when initiating ART in adolescents at SMR III or lower. For recommendations related to pre- (PrEP) and post- (PEP) HIV exposure prophylaxis for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention (CDC).

These guidelines represent current knowledge regarding the use of ARVs. Because the science of HIV evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not always be consistent with approved labeling for the particular drugs or indications, and the use of the terms “safe” and “effective” may not be synonymous with the Food and Drug Administration (FDA)-defined legal standards for drug approval. The Panel frequently updates the guidelines (current and archived versions of the guidelines are available on the AIDSinfo website at http://www.aidsinfo.nih.gov). However, the guidelines cannot always be updated apace with the rapid evolution of new data and cannot offer guidance on care for all patients. Patient management decisions should be based on clinical judgement and attention to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART, and encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials.
### Guidelines Development Process

#### Table 1. Outline of the Guidelines Development Process

<table>
<thead>
<tr>
<th>Topic</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal of the guidelines</strong></td>
<td>Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents (ARVs) for the treatment of HIV in adults and adolescents in the United States.</td>
</tr>
<tr>
<td><strong>Panel members</strong></td>
<td>The Panel is composed of approximately 45 voting members who have expertise in HIV care and research, and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are nongovernmental scientific members. The Panel also includes four to five community members with knowledge in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4 year term with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members.</td>
</tr>
<tr>
<td><strong>Financial disclosure</strong></td>
<td>All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDSinfo website (<a href="http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf">http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf</a>).</td>
</tr>
<tr>
<td><strong>Users of the guidelines</strong></td>
<td>HIV treatment providers</td>
</tr>
<tr>
<td><strong>Developer</strong></td>
<td>Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)</td>
</tr>
<tr>
<td><strong>Funding source</strong></td>
<td>Office of AIDS Research, NIH</td>
</tr>
<tr>
<td><strong>Evidence collection</strong></td>
<td>The recommendations in the guidelines are based on studies published in peer reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.</td>
</tr>
<tr>
<td><strong>Recommendation grading</strong></td>
<td>As described in Table 2</td>
</tr>
<tr>
<td><strong>Method of synthesizing data</strong></td>
<td>Each section of the guidelines is assigned to a working group of Panel members with expertise in the section’s area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines.</td>
</tr>
<tr>
<td><strong>Other guidelines</strong></td>
<td>These guidelines focus on antiretroviral therapy (ART) use for adults and adolescents with HIV. For more detailed discussion on the use of ART for children and prepubertal adolescents (SMR I – III), clinicians should refer to the Pediatric ARV Guidelines. These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women.</td>
</tr>
<tr>
<td><strong>Update plan</strong></td>
<td>The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information that may have an impact on the clinical care of patients. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the AIDSinfo website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDSinfo website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</td>
</tr>
<tr>
<td><strong>Public comments</strong></td>
<td>A 2-week public comment period follows release of the updated guidelines on the AIDSinfo website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at <a href="mailto:contactus@aidsinfo.nih.gov">contactus@aidsinfo.nih.gov</a>.</td>
</tr>
</tbody>
</table>
Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommended statement includes a letter (A, B, or C) that represents the strength of the recommendation and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation (see Table 2).

Table 2. Rating Scheme for Recommendations

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in patients with HIV are better when care is delivered by clinicians with HIV expertise (e.g., care for a larger panel of patients), reflecting the complexity of HIV transmission and its treatment. Appropriate training, continuing education, and clinical experience are all components of optimal care. Providers who do not have this requisite training and experience should consult HIV experts when needed.

References


Baseline Evaluation  (Last updated May 1, 2014; last reviewed May 1, 2014)

Every patient with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and to initiate care as recommended in HIV primary care guidelines1 and guidelines for prevention and treatment of HIV-associated opportunistic infections.2 The initial evaluation also should include discussion on the benefits of antiretroviral therapy (ART) for the patient’s health and to prevent HIV transmission. Baseline information then can be used to define management goals and plans. In the case of previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete antiretroviral (ARV) history (including drug resistance testing results, if available), preferably through the review of past medical records. Newly diagnosed patients should also be asked about any prior use of ARV agents for prevention of HIV infection.

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of ARV drug regimens:

• HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay’s limit of detection) (AI);
• CD4 T lymphocyte cell count (CD4 count) (AI);
• Plasma HIV RNA (viral load) (AI);
• Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN), and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses (AIII);
• Fasting blood glucose and serum lipids (AIII); and
• Genotypic resistance testing (AII). For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful (BII).

In addition, other tests (including screening tests for sexually transmitted infections and tests for determining the risk of opportunistic infections and need for prophylaxis) should be performed as recommended in HIV primary care and opportunistic infections guidelines.1,2

Patients living with HIV infection often must cope with many social, psychiatric, and medical issues that are best addressed through a patient-centered, multi-disciplinary approach to the disease. The baseline evaluation should include an evaluation of the patient’s readiness for ART, including an assessment of high-risk behaviors, substance abuse, social support, mental illness, comorbidities, economic factors (e.g., unstable housing), medical insurance status and adequacy of coverage, and other factors that are known to impair adherence to ART and increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly. The baseline evaluation should also include a discussion of risk reduction and disclosure to sexual and/or needle-sharing partners, especially with untreated patients who are still at high risk of HIV transmission.

Education about HIV risk behaviors and effective strategies to prevent HIV transmission should be provided at each patient visit.

References

Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy  *(Last updated October 25, 2018; last reviewed October 25, 2018)*

Several laboratory tests are important for initial evaluation of patients with HIV upon entry into care, and some tests should be performed before and after initiation or modification of antiretroviral therapy (ART) to assess the virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. Table 3 outlines the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)’s recommendations on the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are routinely used to monitor patients with HIV: CD4 T lymphocyte (CD4) cell count to assess immune function, and plasma HIV RNA (viral load) to assess level of HIV viremia. Resistance testing should be used to guide selection of an ARV regimen. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist. HLA-B*5701 testing should be performed before initiation of abacavir (ABC). Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART and, if indicated, periodically after ART initiation, as treatment of these coinfections may affect the choice of ART. The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the Guidelines.
<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Timepoint or Frequency of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry into Care</td>
</tr>
<tr>
<td>HIV Serology</td>
<td>√</td>
</tr>
<tr>
<td>CD4 Count</td>
<td>√</td>
</tr>
<tr>
<td>HIV Viral Load</td>
<td>√</td>
</tr>
<tr>
<td>Resistance Testing</td>
<td>√</td>
</tr>
<tr>
<td>HLA-B*5701 Testing</td>
<td>√</td>
</tr>
</tbody>
</table>
Table 3. Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapya (page 2 of 3)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Timepoint or Frequency of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry into Care</td>
</tr>
<tr>
<td>Tropism Testing</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)</td>
<td>✓</td>
</tr>
<tr>
<td>Basic Chemistry</td>
<td>✓</td>
</tr>
<tr>
<td>ALT, AST, Total Bilirubin</td>
<td>✓</td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>✓</td>
</tr>
</tbody>
</table>
### Table 3. Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Entry into Care</th>
<th>ART Initiation(^{b}) or Modification</th>
<th>2 to 8 Weeks After ART Initiation or Modification</th>
<th>Every 3 to 6 Months</th>
<th>Every 6 Months</th>
<th>Every 12 Months</th>
<th>Treatment Failure</th>
<th>Clinically Indicated</th>
<th>If ART Initiation is Delayed(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Lipid Profile(^{a})</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
</tr>
<tr>
<td>Fasting Glucose or Hemoglobin A1C</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
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<td>(\surd)</td>
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<td>(\surd)</td>
<td>(\surd)</td>
</tr>
<tr>
<td>Urinalysis(^{m, o})</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
</tr>
<tr>
<td>Pregnancy Test(^{o})</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
<td>(\surd)</td>
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<td>(\surd)</td>
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</table>

\(^{a}\) This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care Guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.\(^{1}\)

\(^{b}\) If ART initiation occurs soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

\(^{c}\) ART is indicated for all individuals with HIV and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

\(^{d}\) If HIV RNA is detectable at 2 to 8 weeks, repeat testing every 4 to 8 weeks until viral load is suppressed to <200 copies/mL. Thereafter, repeat testing every 3 to 6 months.

\(^{m}\) In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

\(^{o}\) Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase and protease genes. If transmitted INSTI resistance is a concern, providers should also test for resistance mutations to this class of drugs. In ART-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if resistance testing was performed at entry into care. In patients with virologic suppression who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; therefore, resistance testing should not be performed. Results from prior resistance testing can be helpful in constructing a new regimen.

\(^{p}\) If patient has HBV infection (as determined by a positive HBsAg or HBV DNA test result), TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections.

\(^{q}\) If HBsAg, HBsAb, and HBcAb test results are negative, hepatitis B vaccine series should be administered. Refer to the HIV Primary Care Guidelines and the Adult and Adolescent Opportunistic Infections Guidelines for detailed recommendations.\(^{1, 2}\)

\(^{r}\) Most patients with isolated HbcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load for confirmation. If the HBV viral load is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If negative, the patient should be vaccinated. Refer to the HIV Primary Care Guidelines and the Adult Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
and Adolescent Opportunistic Infections Guidelines for more detailed recommendations.¹,²

¹ The HCV antibody test may not be adequate for screening in the setting of recent HCV infection (defined as acquisition within the past 6 months), or advanced immunodeficiency (CD4 count <100 cells/mm³). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

² Injection drug users, persons with a history of incarceration, men with HIV who have unprotected sex with men, and persons with percutaneous/parenteral exposure to blood in unregulated settings are at risk of HCV infection.

³ Serum Na, K, HCO₃, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or TDF-containing regimens.³

³ Consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America for recommendations on managing patients with renal disease.³ More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

⁴ Consult the National Lipid Association’s recommendations for management of patients with dyslipidemia.⁴

⁴ Urine glucose and protein should be assessed before initiating TAF- or TDF-containing regimens and monitored during treatment with these regimens.

⁵ This applies to people of childbearing potential.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CD4 = CD4 T lymphocyte; Cl = chloride; DAA = direct-acting antiviral; FTC = emtricitabine; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO₃ = bicarbonate; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
References


Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring  (Last updated May 1, 2014; last reviewed May 1, 2014)

HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell count are the two surrogate markers of antiretroviral treatment (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient’s pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression. The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.

Measurement of CD4 count is particularly useful before initiation of ART. The CD4 cell count provides information on the overall immune function of a person with HIV. The measurement is critical in establishing thresholds for the initiation and discontinuation of opportunistic infection (OI) prophylaxis and in assessing the urgency to initiate ART.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. In the United States, ART is now recommended for all patients with HIV regardless of their viral load or CD4 count (AI) (see Initiation of Antiretroviral Therapy). In the past, clinical practice, which was supported by treatment guidelines, was generally to monitor both CD4 cell count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

Plasma HIV-1 RNA (Viral Load) Monitoring

Viral load is the most important indicator of initial and sustained response to ART (AI) and should be measured in all patients with HIV at entry into care (AIII), at initiation of therapy (AIII), and on a regular basis thereafter. For those patients who choose to delay therapy, repeat viral load testing while not on ART is optional (CIII). Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see What to Start). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see HIV-2 Infection.

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.1-3 Thus, viral load testing is an established surrogate marker for treatment response.4 The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 log10 copies/mL change). Optimal viral suppression is defined generally as a viral load persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not predictive of virologic failure.5 Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One recent study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.6-9 These guidelines and the AIDS Clinical Trials Group (ACTG) now define virologic failure as a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability10 (see Virologic Failure and Suboptimal Immunologic Response).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it
may take longer. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART or modification of therapy because of virologic failure.** Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification (AIII). The purpose of the measurements is to confirm an adequate initial virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay’s limit of detection (BIII).

- **In virologically suppressed patients in whom ART was modified because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy (AIII). The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.

- **In patients on a stable, suppressive ARV regimen.** Viral load should be repeated every 3 to 4 months (AIII) or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable (AIII).

- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen (see Drug-Resistance Testing and Virologic Failure and Suboptimal Immunologic Response sections).

### CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies. CD4 counts are highly variable; a significant change (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it is not routinely recommended (BIII).

**Use of CD4 Count for Initial Assessment**

CD4 count should be measured in all patients at entry into care (AI). It is the key factor in determining the need to initiate OI prophylaxis (see the Adult Opportunistic Infection Guidelines) and the urgency to initiate ART (AI) (see the Initiating Antiretroviral Therapy section of these guidelines). Although most OIs occur in patients with CD4 counts <200 cells/mm³, some OIs can occur in patients with higher CD4 counts.

**Use of CD4 Count for Monitoring Therapeutic Response**

The CD4 count is used to assess a patient’s immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult Opportunistic Infection Guidelines). For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm³ during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 to 100 cells/mm³ per year until a steady state level is reached. Patients who initiate therapy with a low CD4 count or at an older age may have a blunted increase in their counts despite virologic suppression.
Frequency of CD4 Count Monitoring

ART is now recommended for all patients with HIV. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis (AIII).

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution (AIII). This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the guidelines for treatment and prophylaxis of opportunistic infections. In this setting, and in the first 2 years following ART initiation, CD4 count can be monitored at 3- to 6- month intervals (BII).

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 count provides limited information. Frequent testing is unnecessary because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm³ are rare in patients with viral suppression and CD4 counts >300 cells/mm³. Similarly, the ARTEMIS trial found that CD4 monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm³ after 48 weeks of therapy. Furthermore, the risk of Pneumocystis jirovecii pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 and 200 cells/mm³. Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes such as cardiovascular disease, malignancy, and death. An analysis of costs associated with CD4 monitoring in the United States estimated that reducing CD4 monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.

For the patient on a suppressive regimen whose CD4 count has consistently ranged between 300 and 500 cells/mm³ for at least 2 years, the Panel recommends CD4 monitoring on an annual basis (BII). Continued CD4 monitoring for virologically suppressed patients whose CD4 counts have been consistently >500 cells/mm³ for at least 2 years may be considered optional (CIII). The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient’s clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 cell count (e.g., interferon, chronic corticosteroids, or antineoplastic agents) (AIII). In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months (AIII) (see Virologic Failure and Suboptimal Immunologic Response).

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy or coinfection with human T-lymphotropic virus type I (HTLV-1) may cause misleadingly elevated CD4 counts. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient’s immune function.
### Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Viral Load Monitoring</th>
<th>CD4 Count Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before initiating ART</td>
<td>At entry into care (AIII)</td>
<td>At entry into care (AII)</td>
</tr>
<tr>
<td></td>
<td>If ART initiation is deferred, repeat before initiating ART (AIII)</td>
<td>If ART is deferred, every 3 to 6 months (AIII)</td>
</tr>
<tr>
<td></td>
<td>In patients not initiating ART, repeat testing is optional (CIII)</td>
<td></td>
</tr>
<tr>
<td>After initiating ART</td>
<td>Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII).</td>
<td>3 months after initiation of ART (AIII)</td>
</tr>
<tr>
<td>After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression</td>
<td>4 to 8 weeks after modification of ART to confirm effectiveness of new regimen (AIII).</td>
<td>Monitor according to prior CD4 count and duration on ART, as outlined below.</td>
</tr>
<tr>
<td>After modifying ART because of virologic failure</td>
<td>Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII). If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated (AIII).</td>
<td>Every 3 to 6 months (AIII)</td>
</tr>
<tr>
<td>During the first 2 years of ART</td>
<td>Every 3 to 4 months (AIII)</td>
<td>Every 3 to 6 months (BII)</td>
</tr>
<tr>
<td>After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm³)</td>
<td>Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).</td>
<td>Every 12 months (BII)</td>
</tr>
<tr>
<td>After 2 years of ART (VL consistently suppressed, CD4 consistently &gt;500 cells/mm³)</td>
<td></td>
<td>Optional (CIII)</td>
</tr>
<tr>
<td>While on ART with detectable viremia (VL repeatedly &gt;200 copies/mL)</td>
<td>Every 3 months (AIII) or more frequently if clinically indicated (see Virologic Failure).</td>
<td>Every 3 to 6 months (AIII)</td>
</tr>
<tr>
<td>Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)</td>
<td>Every 3 months (AIII)</td>
<td>Perform CD4 count and repeat as clinically indicated (AIII)</td>
</tr>
</tbody>
</table>

* Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended (BIII).

* Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm³) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm³).

* The following are examples of clinically indicated scenarios: changes in a patient’s clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

### References


10. Ribaudo H, Lennox J, Currier J, al e. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada.


Drug-Resistance Testing  *(Last updated October 25, 2018; last reviewed October 25, 2018)*

### Panel's Recommendations

#### For Antiretroviral Therapy-Naive Persons:
- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen *(AII)*. If therapy is deferred, repeat testing may be considered at the time of ART initiation *(CII)*.
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients *(AII)*.
- In persons with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported *(AII)*.
- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes the integrase gene *(AIII)*.

#### For Antiretroviral Therapy-Experienced Persons:
- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ART regimens in the following patients:
  - Persons with virologic failure and HIV RNA levels >1,000 copies/mL *(AI)*
  - Persons with HIV RNA levels >500 copies/mL but <1,000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered *(BII)*
  - Persons with suboptimal viral load reduction *(AII)*
  - When a person with HIV experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance (which may need to be ordered separately) should be performed to determine whether to include a drug from this class in subsequent regimens *(AII)*.
- Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if that is not possible, within 4 weeks after discontinuing therapy *(AII)*. If more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed due to lack of drug-selective pressure *(CII)*.
- Genotypic testing is preferred over phenotypic resistance testing to guide therapy in persons with suboptimal virologic response or virologic failure while on first- or second-line regimens and in individuals in whom resistance mutation patterns are known or not expected to be complex *(AII)*.
- The addition of phenotypic to genotypic resistance testing is recommended for persons with known or suspected complex drug-resistance mutation patterns *(BII)*.
- All prior and current drug-resistance test results, if available, should be considered when constructing a new regimen for a patient *(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

**Genotypic and Phenotypic Resistance Assays**

Genotypic and phenotypic resistance assays are used to assess viral strains and select treatment strategies. These assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). In some circumstances, INSTI-resistance tests may need to be ordered separately, and clinicians should check this with the testing laboratory. INSTI-resistance testing is particularly important in persons who experience virologic failure while taking an INSTI-containing regimen. Testing for fusion inhibitor resistance can also be ordered separately. There is currently no commercially available resistance test for the CD4 T lymphocyte post-attachment inhibitor ibalizumab. For a description of co-receptor tropism testing, see Co-receptor Tropism Assays.
Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes; in general, these assays require a plasma viral load of at least 500 to 1,000 copies/mL. Most genotypic assays involve conventional Sanger sequencing of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes of circulating RNA in plasma to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene associated with resistance to the fusion inhibitor enfuvirtide is also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpreting these test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains an updated list of significant resistance-associated mutations in the RT, PR, IN, and envelope genes. The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results. Various additional tools are also available to assist providers in interpreting genotypic test results. Clinical trials have demonstrated that consulting with specialists in HIV drug resistance improves virologic outcomes. Clinicians are thus encouraged to consult a specialist to interpret genotypic test results and design optimal new regimens.

A next-generation sequencing genotypic resistance assay that analyzes HIV-1 proviral DNA in host cells is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection or with low-level viremia.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT, PR, and, more recently, IN and envelope gene sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [IC₅₀]) is calculated, and the ratio of the IC₅₀ of test and reference viruses is reported as the fold increase in IC₅₀ (i.e., fold resistance).

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpreting phenotypic assay results can be complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC₅₀) associated with drug failure, although clinically significant fold increase cutoffs have been described for some drugs. Again, consulting with a specialist to interpret test results can be helpful.

Limitations of Genotypic and Phenotypic Assays

Limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important to note because a wild-type virus often re-emerges as the predominant population in the plasma after discontinuation of drugs that exert selective pressure on drug-resistant populations. As a consequence, the proportion of virus with resistance mutations can decrease to below the 10% to 20% threshold. In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus. Therefore, resistance testing is most valuable when performed while a person experiencing virologic failure is still taking ARV drugs or, if that is not possible,
then within 4 weeks after discontinuing therapy (AII). Because resistant viruses may persist longer in the plasma of some patients, resistance testing that is done 4 to 6 weeks after discontinuation of drugs or later may still detect mutations and provide useful information to guide therapy (CIII). However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens. Importantly, in addition to considering prior antiretroviral therapy (ART) history, prior genotypic- or phenotypic-resistance test results should be obtained from old records when possible. Because the most current drug-resistance test may not be able to detect resistance mutations that were previously detected, these prior test results are clinically important and should be used when designing a new regimen (AIII).

A next-generation sequencing genotypic assay that analyzes HIV-1 proviral DNA may provide additional information on drug resistance in patients with low levels of plasma HIV RNA or in patients whose levels are below the limit of detection (CIII). However, these assays might miss some or all the previous drug-resistance mutations, and they should be interpreted with caution. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Clinical Practice (See Table 5)

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART.16-19 The risk of acquiring drug-resistant virus is related to the prevalence of drug resistance in people with HIV who engage in high-risk behaviors within a given community. In high-income countries, approximately 10% to 17% of ART-naive individuals have resistance mutations to at least one ARV drug.20 Up to 8%, but generally <5%, of transmitted viruses will exhibit resistance to drugs from more than one class.20-23 Transmitted resistant HIV is generally either NNRTI- or NRTI-resistant. Transmitted PI resistance is much less common, and to date, transmitted INSTI resistance is rare.24,25

Resistance testing can guide therapy selection to optimize virologic response in people with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis. Therefore, resistance testing in these situations is recommended (AII). A genotypic assay is preferred for this purpose (AIII). In these settings, treatment initiation should not be delayed pending resistance testing results if the individual is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see also Acute and Recent HIV [Early] Infection). In the absence of ART, resistant viruses may decline over time to less than the detection limit of standard resistance tests. However, when ART is eventually initiated, even low levels of resistant viruses may still increase the risk of treatment failure.26-28 Therefore, if ART is deferred, resistance testing should still be performed during early HIV infection (AIII). In this situation, the genotypic resistance test result should be used for regimen selection when the person begins ART. Repeat resistance testing at the start of treatment may also be considered, because a patient may acquire drug-resistant virus (i.e., superinfection) between entry-into-care and the initiation of ART (CIII).28

Interpretation of drug-resistance testing before ART initiation in persons with chronic HIV is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.30-32 Though no prospective trial has directly addressed whether drug-resistance testing before initiation of therapy confers benefit in this population, data from several studies, including one prospective clinical trial, suggest that virologic responses in persons with baseline resistance mutations are suboptimal.16-19,33-38 In addition, an analysis of early RT and PR genotypic resistance testing in ARV-naive persons suggests that baseline testing in this population is cost effective and should be performed.38 Therefore, resistance testing in people with chronic infections is recommended at the time of entry into HIV care (AII).
Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred over phenotypic testing because of lower cost, more rapid turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier interpretation of test results (AIII). If therapy is deferred, repeat testing shortly before initiating ART may be considered, because the patient may have acquired drug-resistant virus (i.e., superinfection) (CIII).

Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the RT and PR genes. Although reports of transmission of INSTI-resistant virus are rare, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers should supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs, which may need to be ordered separately (AIII).

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA in host cells can be considered when conventional HIV RNA drug resistance testing is unsuccessful or unavailable for patients initiating therapy (CIII). As outlined above, the results should be interpreted with caution, as this assay might miss some or all previously existing drug-resistance mutations.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are important tools to inform treatment decisions for patients who experience virologic failure while on ART. Several prospective studies have assessed the utility of resistance testing to guide ARV drug selection in patients who experience virologic failure. These studies involved genotypic assays, phenotypic assays, or both. In general, these studies found that changes in therapy based on resistance test results produced better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that the use of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival. Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL (AI) (see also Virologic Failure). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII). Conventional drug-resistance testing in persons with plasma viral loads <500 copies/mL is not usually recommended, because resistance assays cannot be consistently performed at low HIV RNA levels (AIII).

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction (AII). Virologic failure in the setting of ART is, for certain patients, associated with resistance to only one component of the regimen. In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotyping is preferred for resistance testing in patients who experience virologic failure or suboptimal viral load reduction while on a first or second ARV drug regimen and in individuals in whom resistance mutation patterns are known or not expected to be complex (i.e., mutations that are straightforward, usually limited in number, and/or those that have clear significance) (AII). Often in these situations, the mutation patterns detected can be interpreted by algorithms used to predict the impact of subsequent regimens on virologic response. For patients with extensive treatment history, complex mutational patterns may occur. In such situations, the interpretation of complex genotypes and the impact of the mutation pattern on subsequent treatment regimens can be challenging. For these individuals, phenotypic resistance testing may provide additional helpful information (BIII). Rather than only predicting the impact of the detected mutations, these assays can measure in vitro the actual fold change in drug susceptibility, as well as the actual impact of mutation combinations and interactions on each drug under consideration.

When compared with phenotypic testing, genotypic testing costs less to perform and has a faster turnaround time.
and greater sensitivity for detecting mixtures of wild-type and resistant virus. In addition, observations show that genotypic and phenotypic assays are comparable predictors of virologic response to subsequent ART regimens.\textsuperscript{50} In patients who experience virologic failure while on INSTI-based regimens, testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII). In this circumstance, clinicians should confirm that, when they order a resistance test, their laboratory is testing for INSTI resistance in addition to NNRTI, NRTI, and PI resistance. If INSTI-resistance testing needs to be ordered separately (as is the case in some laboratories), clinicians should request this assay in addition to standard drug-resistance testing. Addition of phenotypic to genotypic testing is generally indicated for persons with known or suspected complex drug-resistance mutation patterns (BIII).

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for patients who are experiencing treatment failure and for whom conventional HIV RNA genotypic drug-resistance testing is unavailable or unsuccessful (CIII). As outlined above, results should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed (AI) (see Co-receptor Tropism Assays).

Use of Resistance Assays for Optimizing Antiretroviral Regimen in Persons with Viral Suppression

In the past decade, simpler, more potent, and better-tolerated ARV medications have become available and new ARV drugs will likely continue to emerge. Switching individual ARV drugs in a regimen is sometimes considered for patients with a suppressed viral load in order to simplify a regimen, avoid drug interactions or toxicity, or for other reasons. Because the patient’s viral load is suppressed, standard drug-resistance testing will not be successful.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for these individuals, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals who have experienced no prior virologic failures and who are on their first or second regimen, or who have genotypic testing results from when they had prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide additional useful information. However, in individuals who have experienced multiple prior failures, a prolonged history of prior ARV regimens, and/or for whom prior genotypic resistance test results are not available, it may be appropriate to utilize proviral DNA genotypic testing (CIII). When such testing is obtained, results should be combined with all prior genotypic and phenotypic test results to construct a cumulative genotype, which incorporates all current and previously detected drug-resistance mutations. Results from this test should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Pregnancy

In pregnancy, the goal of ART is to rapidly and maximally reduce plasma HIV RNA to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant persons with HIV before initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI). Phenotypic testing in those found to have complex drug-resistance mutation patterns may provide additional information (BIII). Optimal prevention of perinatal transmission requires prompt initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.
### Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

<table>
<thead>
<tr>
<th>Clinical Setting and Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Acute or Recent (Early) HIV Infection:</strong> Drug-resistance testing is recommended (AII). A genotypic assay is generally preferred (AIII). Treatment should not be delayed while awaiting results of resistance testing (AIII).</td>
<td>Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified, if necessary, once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.</td>
</tr>
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<td>If ART is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AII).</td>
<td>Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).</td>
</tr>
<tr>
<td><strong>In ART-Naive Patients with Chronic HIV:</strong> Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART (AII). A genotypic assay is generally preferred (AIII).</td>
<td>Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV.</td>
</tr>
<tr>
<td>For pregnant persons, or if ART will be initiated on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.</td>
<td>If necessary, the ART regimen can be modified once resistance test results are available.</td>
</tr>
<tr>
<td>If an INSTI is considered for an ART-naive patient and/or transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately (AIII).</td>
<td>Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings.</td>
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<td>If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred (AIII).</td>
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<td>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed (AII).</td>
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<td><strong>In Patients with Virologic Failure:</strong> Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels &gt;1,000 copies/mL (AII). In patients with HIV RNA levels &gt;500 copies/mL but &lt;1,000 copies/mL, testing may not be successful but should still be considered (BII). Resistance testing should be done while the patient is taking ART, or, if that is not possible, within 4 weeks after ART discontinuation (AII). If &gt;4 weeks have elapsed, resistance testing may still be useful to guide therapy; however, previously-selected mutations can be missed due to lack of drug selective pressure (CIII). A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimen and for those with noncomplex resistance patterns (AII).</td>
<td>Drug-resistance testing can help determine the role of resistance in drug failure and maximize the clinician’s ability to select active drugs for the new regimen.</td>
</tr>
<tr>
<td>All prior and current drug-resistance testing results should be reviewed and considered when designing a new regimen for a patient experiencing virologic failure (AII). When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII).</td>
<td>The absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens, as mutations may decay with time.</td>
</tr>
<tr>
<td>Drug resistance mutations may decay with time, and mutations detected in prior resistance tests may not be detected in current tests, though they remain clinically relevant.</td>
<td>Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory).</td>
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<td>Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified, if necessary, once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.</td>
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<td>If ART is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AII).</td>
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<td><strong>In ART-Naive Patients with Chronic HIV:</strong> Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART (AII). A genotypic assay is generally preferred (AIII).</td>
<td>Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV.</td>
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<td>For pregnant persons, or if ART will be initiated on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.</td>
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<td>If an INSTI is considered for an ART-naive patient and/or transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately (AIII).</td>
<td>Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory). Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings.</td>
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<td>If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred (AIII).</td>
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*Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV* C-18

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Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

<table>
<thead>
<tr>
<th>Clinical Setting and Recommendation</th>
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<td>Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns (BIII).</td>
<td>Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns.</td>
</tr>
<tr>
<td>In Patients with Suboptimal Suppression of Viral Load: Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART (AII).</td>
<td>Testing can determine the role of resistance in suboptimal viral suppression, and it can help the clinician identify the number of active drugs available in the current regimen and assess the need for a new regimen.</td>
</tr>
<tr>
<td>In Pregnant Persons with HIV: Genotypic resistance testing is recommended for all pregnant persons before initiation of ART (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).</td>
<td>The goals of ART in pregnant persons with HIV are to achieve maximal viral suppression for treatment of maternal HIV and to prevent perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available, if needed.</td>
</tr>
<tr>
<td>In Patients with Undetectable Viral Load or Low-Level Viremia: HIV-1 proviral DNA resistance assays may be useful in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV RNA genotypic assay is unlikely to be successful (CIII).</td>
<td>This test may provide information about previously circulating resistant viral variants that are archived within proviral DNA. These assays may miss some or all prior resistance mutations that have occurred within the viral quasi-species, and therefore they should be interpreted with caution. The clinical utility of HIV-1 proviral DNA assays has not been fully determined.</td>
</tr>
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Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

References


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HIV enters cells by a complex process that involves sequential attachment to the CD4 T lymphocyte (CD4) receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes.1 CCR5 co-receptor antagonists prevent HIV entry into target cells by binding to the CCR5 receptors.2 Phenotypic and genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., use of CCR5, CXCR4, or both as either dual-tropic virus or a mixed population of viruses referred to for purposes of assay results as dual/mixed [D/M]) of the patient’s dominant virus population. An older generation assay (Trofile®, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in clinical trials that led to the approval of maraviroc (MVC), the only CCR5 antagonist currently available. The assay has been improved and is now available with enhanced sensitivity. In addition, genotypic assays to predict co-receptor usage are commercially available.

During acute/recent infection, the vast majority of patients harbor a CCR5-utilizing virus (R5 virus), which suggests that the R5 variant is preferentially transmitted; however, up to 19% of individuals with acute/recent infection can harbor CXCR4-tropic virus.3-5 Viruses in many untreated patients eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 usage or D/M tropism. This shift is temporally associated with a more rapid decline in CD4 counts,6,7 but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.1 Antiretroviral-treated patients with extensive drug resistance or persistently high-level viremia are more likely to harbor CXCR4- or D/M-tropic variants than untreated patients with comparable CD4 counts.8,9 The prevalence of CXCR4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm3.8,10 Since CXCR4-tropic viruses may be present at initial presentation or a patient may shift to CXCR4-tropism over the course of infection, co-receptor tropism should always be assessed prior to the use of CCR5 antagonists for treatment. Once a patient has ever been documented with detectable CXCR4- or D/M-tropic virus, it is assumed that such viruses will always be present. CCR5 co-receptor antagonists will no longer be active for that patient and should not be used.

**Phenotypic Assays**

Phenotypic assays characterize the co-receptor usage of plasma-derived virus. These assays involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses, which are replication-defective, are used to infect target cell lines that express either CCR5 or CXCR4.11,12 Using the Trofile® assay, the co-receptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors in vitro. This assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

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### Panel’s Recommendations

- A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered (AI).
- Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist (BIII).
- A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage (AI).
- A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage (BII).
- A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) (BII).

**Rating of Recommendations:**

- A = Strong; B = Moderate; C = Optional

**Rating of Evidence:**

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

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The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the Trofile® assay. This earlier assay failed to routinely detect low levels of CXCR4 utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low levels of such variants at baseline, which were below the assay limit of detection, and these patients exhibited rapid virologic failure after initiation of a CCR5 antagonist. The assay has been improved and is now able to detect lower levels of CXCR4-utilizing viruses. In vitro, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones represent 0.3% or more of the virus population. Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only assay that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the Trofile® assay.

In patients with an undetectable viral load or detectable plasma HIV RNA <1,000 copies/mL, phenotypic co-receptor usage can be determined using proviral DNA obtained from peripheral blood mononuclear cells (e.g., Trofile® DNA, Monogram Sciences); however, the clinical utility of this assay remains to be determined.

**Genotypic Assays**

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 env, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50% to 75%) for the presence of a CXCR4-utilizing virus. Studies in which V3 genotyping was performed on samples from patients screened for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC. An important caveat is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (Trofile®). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. Other studies have also demonstrated relatively high concordance between genotypic- and phenotypic-assessed tropism; however, there is variability between different genotypic platforms.

Given these performance characteristics, genotypic tropism assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant; therefore, the Panel preferentially recommends phenotypic testing. Based on accessibility, capacity, logistics, and cost, European guidelines currently include genotypic testing as an equivalent option to phenotypic testing when determining co-receptor usage among patients with HIV RNA >1,000 copies/mL and preferentially for those with HIV RNA ≤1,000 copies/mL.

HIV-1 proviral DNA genotypic tropism testing is available for patients with HIV RNA <1,000 copies/mL. These assays evaluate the HIV-1 proviral DNA integrated within infected cells for CXCR4-utilizing viral strains. As discussed above, caution is advised when using such assays, as their detection limit, concordance with plasma HIV RNA tropism, and clinical utility are not yet fully determined.

**Use of Assays to Determine Co-receptor Usage in Clinical Practice**

An assay for HIV-1 co-receptor usage should be performed whenever the use of a CCR5 antagonist is being considered (AI). This is true even in the setting of prior tropism testing showing CCR5 usage, as viral evolution may occur over the course of infection. In addition, because virologic failure may occur due to a shift from CCR5-using to CXCR4-using virus, testing for co-receptor usage is recommended in patients who exhibit virologic failure on a CCR5 antagonist (BIII). Virologic failure may also be caused by resistance of a CCR5-using virus to a CCR5 antagonist, but such resistance is uncommon. Compared to genotypic testing, phenotypic testing has more evidence supporting its utility. Therefore, a phenotypic test for co-receptor usage is generally preferred (AI). However, because phenotypic testing is more expensive, requires more time to
perform, and may have logistic challenges, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test (BII).

As with HIV resistance testing, the results of all prior tropism tests should be obtained. If CXCR4-utilizing or D/M-tropic viruses have ever been detected previously, then repeat testing is not necessary and a CCR5 co-receptor antagonist should not be used.

If a CCR5 co-receptor antagonist is being considered in a patient with an undetectable HIV RNA (e.g., in cases of regimen simplification or a toxicity-related switch), a proviral DNA tropism assay can be utilized (BII). If CXCR4-utilizing or D/M-tropic viruses are detected, then the CCR5 co-receptor antagonist should not be used.

References


The abacavir (ABC) hypersensitivity reaction (HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5% to 8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.1

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701.2,3 Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR.4 A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele.5 The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool.

The PREDICT-1 study randomized participants with HIV before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC).6 The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations).7

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting an ABC-containing regimen in a person with HIV (AI). HLA-B*5701–positive patients should not be prescribed ABC (Al), and the positive status should be recorded as an ABC allergy in the patient’s medical record (AII). HLA-B*5701 testing is needed only once in a patient’s lifetime; thus, efforts to carefully record and maintain the test result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701–positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening
is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR (CIII).

References


**Treatment Goals** *(Last updated January 28, 2016; last reviewed January 28, 2016)*

Antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality at all stages of HIV infection\(^1^-^4\) and has reduced HIV transmission.\(^5^-^8\) Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 T lymphocyte (CD4) cell numbers, and confers substantial clinical benefits, all of which are important treatment goals.\(^9^-^10\) HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in cohorts with HIV (see *Initiating Antiretroviral Therapy*). Despite these benefits, eradication of HIV infection cannot be achieved with available antiretrovirals (ARVs). Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality.\(^11\) Thus, once initiated, ART should be continued, with the following key treatment goals:

- Maximally and durably suppress plasma HIV RNA;
- Restore and preserve immunologic function;
- Reduce HIV-associated morbidity and prolong the duration and quality of survival; and
- Prevent HIV transmission.

Achieving viral suppression currently requires the use of combination ARV regimens that generally include three active drugs from two or more drug classes. Baseline patient characteristics and results from drug resistance testing should guide design of the specific regimen (see *What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient*). When initial HIV suppression is not achieved or not maintained, changing to a new regimen with at least two active drugs is often required (see *Virologic Failure*). The increasing number of ARV drugs and drug classes makes viral suppression below detection limits an achievable goal in most patients.

After initiation of effective ART, viral load reduction to below limits of assay detection usually occurs within the first 12 to 24 weeks of therapy. Predictors of virologic success include the following:

- Low baseline viremia;
- High potency of the ARV regimen;
- Tolerability of the regimen;
- Convenience of the regimen; and
- Excellent adherence to the regimen.

**Strategies to Achieve Treatment Goals**

**Selection of Initial Combination Regimen**

Several ARV regimens are recommended for use in ART-naive patients (see *What to Start*). Most of the recommended regimens have comparable efficacy but vary in pill burden, potential for drug interactions and/or side effects, and propensity to select for resistance mutations if ART adherence is suboptimal. Regimens should be tailored for the individual patient to enhance adherence and support long-term treatment success. Considerations when selecting an ARV regimen for an individual patient include potential side effects, patient comorbidities, possible interactions with concomitant medications, results of pretreatment genotypic drug-resistance testing, and regimen convenience (see *Table 7*).

**Improving Adherence**

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient-related factors, such as active substance abuse, depression, or
the experience of adverse effects; and health system issues, including interruptions in patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART (see Adherence to the Continuum of Care).

References


Initiation of Antiretroviral Therapy  (Last updated October 17, 2017; last reviewed October 17, 2017)

Panel’s Recommendations

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

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

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

Introduction

Without antiretroviral therapy (ART), most individuals with HIV will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death. The primary goal of ART is to prevent HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication to sustain plasma HIV-1 RNA (viral load) below limits of quantification by commercially available assays. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life.

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

Historically, individuals with HIV have had low CD4 counts at presentation to care.4 However, there have been concerted efforts to increase testing of at-risk individuals and to link individuals with HIV to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining and certain serious non-AIDS conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm³ never achieve CD4 counts >500 cells/mm³ after up to 10 years on ART5,6 and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.5-7

Two large, randomized controlled trials that addressed the optimal time to initiate ART—START8 and TEMPRANO9—demonstrated approximately a 50% reduction in morbidity and mortality among individuals with HIV who had CD4 counts >500 cells/mm³ and who were randomized to receive ART immediately versus delaying initiation of ART (described in more detail below). The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) therefore recommends immediate initiation of ART for all people living with HIV, regardless of CD4 count (AI). Prompt initiation of ART is particularly important for patients with certain clinical conditions, as discussed below.

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

Panel’s Recommendations

ART is recommended for all individuals with HIV, regardless of CD4 cell count, to reduce the morbidity and
mortality associated with HIV infection (AI). ART is also recommended for individuals with HIV to prevent HIV transmission (AI). When initiating ART, it is important to educate patients about the benefits of ART, and to address barriers to adherence and recommend strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors; however, therapy should be initiated as soon as possible. Patients should also understand that currently available ART does not cure HIV. To improve and maintain immunologic function and maintain viral suppression, ART should be continued indefinitely.

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

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

**Acute Opportunistic Infections and Malignancies**

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

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

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

Clinicians should refer to the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents\footnote{14} for more detailed discussion on when to initiate ART in the setting of a specific OI.
The Need for Early Diagnosis of HIV

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

Evidence Supporting Benefits of Antiretroviral Therapy to Prevent Morbidity and Mortality

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

The START trial is a large, multi-national, randomized controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV in reducing a composite clinical endpoint of AIDS-defining illnesses, serious non-AIDS events, or death. In this study, ART-naive adults (aged >18 years) with CD4 counts >500 cells/mm\textsuperscript{3} were randomized to initiate ART soon after randomization (immediate-initiation arm) or to wait to initiate ART until their CD4 counts declined to <350 cells/mm\textsuperscript{3} or until they developed a clinical indication for therapy (deferred-initiation arm). The study enrolled 4,685 participants, with a mean follow-up of 3 years. When the randomized arms of the study were closed, the primary endpoint of serious AIDS or non-AIDS events was reported in 42 participants (1.8%, or 0.60 events/100 person-years) in the immediate ART arm and 96 participants (4.1%, or 1.38 events/100 person-years) in the deferred ART arm (hazard ratio [HR] 0.43, favoring early ART [95% confidence interval (CI), 0.30–0.62, \(P < .001\)]). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies. The majority (59%) of clinical events in the deferred ART arm occurred in participants whose CD4 counts were still above 500 cells/mm\textsuperscript{3}, evidence for a benefit of immediate ART even before CD4 count declines below this threshold. Furthermore, the benefit of immediate ART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate ART for each category of clinical events, the benefit of immediate ART appeared to be particularly strong for AIDS events (HR 0.28, [95% CI, 0.15–0.50, \(P < .001\)]), tuberculosis (HR 0.29, [95% CI, 0.12–0.73, \(P = .008\)]), and malignancies (HR 0.36, [95% CI, 0.19 to 0.66; \(P = .001\)]). Importantly, immediate ART also significantly reduced the rate of pooled serious non-AIDS events (HR0.61, [95% CI, 0.38–0.97, \(P = 0.04\)]).\textsuperscript{8}

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d’Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm\textsuperscript{3} were randomized...
to either immediate ART or deferred ART (based on the national guidelines criteria for starting treatment); half of the participants in each group received isoniazid for prevention of tuberculosis for 6 months and half did not. The primary study endpoint was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases. More than 2,000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 counts >500 cells/mm³, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favor of early ART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early ART is beneficial in reducing the rate of these clinical events.9

The TEMPRANO and START trials had very similar estimates of the protective effect of immediate ART among individuals with HIV who had CD4 counts >500 cells/mm³, further strengthening the Panel’s recommendation that ART be initiated in all patients regardless of CD4 cell count.

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

While the START and TEMPRANO studies demonstrated a clear benefit of immediate ART initiation in individuals with CD4 cell counts >500 cells/mm³, it is plausible that the benefits of early ART initiation continue long after viral suppression is achieved. As detailed in the Poor CD4 Cell Recovery and Persistent Inflammation section, persistently low CD4 counts and abnormally high levels of immune activation and inflammation despite suppressive ART predict an increased risk of not only AIDS events, but also non-AIDS events including kidney disease, liver disease, cardiovascular disease, neurologic complications, and malignancies. Earlier ART initiation appears to increase the probability of restoring normal CD4 counts, a normal CD4/CD8 ratio, and lower levels of immune activation and inflammation.34-39 Individuals initiating ART very early (i.e., during the first 6 months after infection) also appear to achieve lower immune activation levels and better immune function (as assessed by vaccine responsiveness) during ART-mediated viral suppression than those who delay therapy for a few years or more.40-42 Thus, while these questions have yet to be addressed in definitive randomized controlled trials, earlier ART initiation may result in less residual immune dysfunction during treatment, which theoretically may result in reduced risk of disease for decades to come.

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

**Prevention of Sexual Transmission**

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

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the partner with HIV was ART naive with a CD4 count of 350 to 550 cells/mm³ at enrollment to compare the effect of immediate ART versus delayed therapy (not started until CD4 count <250 cells/mm³) on HIV transmission to the partner who did not have HIV.45 At study entry, 97% of the participants reported to be in a heterosexual monogamous relationship. All study participants were counseled on behavioral modification and condom use. The interim results reported 28 linked HIV transmission events during the study period, with only one event in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04; 95% CI, 0.01–0.27; P < 0.001). The final results of this study showed a sustained 93% reduction of HIV transmission within couples when the partner with HIV was taking ART as prescribed and viral load was suppressed.2 Notably, there were only eight cases of HIV transmission within couples after the partner with HIV started ART; four transmissions occurred before the partner with HIV...
was virologically suppressed and four other transmissions occurred during virologic failure. These results provide evidence that suppressive ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission. HPTN 052 was conducted in heterosexual couples and not in populations at risk of HIV transmission via male-to-male sexual contact or needle sharing. In addition, in this clinical trial, adherence to ART was excellent. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to individuals who are at risk of transmitting HIV to sexual partners (AI). Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen. Clinicians should also stress that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STIs.

**Prevention of Perinatal Transmission**

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

**Considerations When Initiating Antiretroviral Therapy**

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

**Optimizing Adherence and Retention in Care**

The key to successful ART in maintaining viral suppression is adherence to the prescribed regimen. Treatment failure and resultant emergence of drug resistance mutations may compromise future treatment options. While optimizing adherence and linkage to care are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier. In both the START and TEMPRANO trials, participants randomized to immediate ART achieved higher rates of viral suppression than those randomized to delayed ART. Nevertheless, it is important to discuss strategies to optimize adherence and retention in care with patients before ART initiation.

Several clinical, behavioral, and social factors have been associated with poor adherence. These factors include untreated major psychiatric disorders, neurocognitive impairment, active substance abuse, unstable housing, other unfavorable social circumstances, patient concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in Adherence to the Continuum of Care. Nevertheless, clinicians are often inaccurate in predicting ART adherence and ART reduces morbidity and mortality even in patients with relatively poor adherence and established drug resistance. Thus, mental illness, substance abuse, and psychosocial challenges are not reasons to withhold ART from a patient. Rather, these issues indicate the need for additional interventions to support adherence.
Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

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

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as “elite HIV controllers.” There are limited data on the role of ART in these individuals. Given the clear benefit of ART regardless of CD4 count from the START and TEMPRANO studies, delaying ART to see if a patient becomes an elite controller after initial diagnosis is strongly discouraged. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years. Given that ongoing HIV replication occurs even in elite controllers, ART is clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications. Nonetheless, even elite controllers with normal CD4 counts also have evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS related diseases. One observational study suggests that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients. Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial. Whether this potential immunologic benefit of ART in elite controllers outweighs potential ART toxicity and results in clinical benefit is unclear. Unfortunately, randomized controlled trials to address this question are unlikely, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population. Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.
Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel’s recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults. Historically, compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression. Because youth often face multiple psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to accepting and adhering to therapy. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support (see Adolescents with HIV).

Conclusion

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

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Panel’s Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).

- A pregnancy test should be performed for those of childbearing potential prior to the initiation of antiretroviral therapy (AIII).

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as Recommended Initial Regimens for Most People with HIV (in alphabetical order):
  - Bictegravir/tenofovir alafenamide/emtricitabine (AI)
  - Dolutegravir/abacavir/lamivudine—a only for patients who are HLA-B*5701 negative (AI)
  - Dolutegravir (DTG) plus tenofovir/emtricitabine (AI)
  - Raltegravir plus tenofovir/emtricitabine—a (BI for tenofovir disoproxil fumarate, BII for tenofovir alafenamide)

- Preliminary data have raised concerns about an increased risk of neural tube defects in infants born to people who were receiving DTG at the time of conception. Before prescribing DTG or another INSTI, please refer to Table 6b for specific recommendations on initiating these drugs as part of initial therapy.

- To address individual patient characteristics and needs, the Panel also provides a list of Recommended Initial Regimens in Certain Clinical Situations (Table 6a).

- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 9 highlights the advantages and disadvantages of different components in a regimen.

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

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

*Lamivudine may substitute for emtricitabine or vice versa.

*Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are two forms of tenofovir that are approved by the Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Introduction

More than 30 antiretroviral (ARV) drugs in seven mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These seven classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, and a CD4 post-attachment inhibitor. In addition, two drugs, ritonavir (RTV or r) and cobicistat (COBI or c) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of some ARV drugs (e.g., PIs and the INSTI elvitegravir [EVG]).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate (TDF)/FTC, plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 T lymphocyte (CD4) cell count increases in most persons with HIV. Emerging data support the use of two-drug regimens, such as
dolutegravir (DTG) plus 3TC, when ABC, TDF, and TAF cannot be used or are not optimal (see the section below titled Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal).

Supporting Evidence and Rationale Used for the Panel’s Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)’s recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen produces high rates of viral suppression, increases CD4 count, and has a favorable safety profile to be the strongest evidence on which to base recommendations. Comparative clinical trials of initial treatments generally show no significant differences in HIV-related clinical endpoints or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include medications approved by the FDA based on bioequivalence or relative bioavailability studies demonstrating that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s) that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies, in which a new medication replaces an existing medication from the same class in patients who have achieved virologic suppression on an initial regimen. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen’s ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. In this section of the guidelines, the definition of an evidence rating of II is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, post-marketing safety data, observational cohort data published in peer-reviewed publications, and the experience of clinicians and community members who are actively engaged in patient care.

The Panel reviewed the available data to arrive at two regimen classifications for ARV-naive patients: (1) Recommended Initial Regimens for Most People with HIV and (2) Recommended Initial Regimens in Certain Clinical Situations (Table 6a). Recommended Initial Regimens for Most People with HIV are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that, in certain clinical situations, other regimens may be preferred; these options are included in Table 6a in the category of Recommended Initial Regimens in Certain Clinical Situations. Examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous are outlined in Table 7.

There are many other ARV regimens that are effective for initial therapy but have disadvantages when compared with the regimens listed in Table 6a. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These other regimens are no longer included in Table 6a. A person with HIV who is virologically suppressed and who is not experiencing any adverse effects on a regimen that is not listed in Table 6a need not necessarily change to a regimen that is in that table. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.
Regimens and medications listed in Table 10 are not recommended as initial ARV. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables presented below and at the end of these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 1–7 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 8 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.

**Changes Since the Last Revision of the Guidelines**

Since the last revision of the Adult and Adolescent Guidelines, there have been several important changes in the Panel’s recommendations for initial therapy in people with HIV. Among these changes, the following deserve particular emphasis:

**INSTI-Based Regimens as Initial Antiretroviral Therapy:**

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

**NNRTI-Based Regimens as Initial Antiretroviral Therapy:**

- The regimen of doravirine (DOR) plus TDF/3TC or TAF/FTC has been added to the category of Recommended Initial Regimens in Certain Clinical Situations. DOR is a new NNRTI that was recently approved for use in ART-naive individuals when administered with two NRTIs. DOR/TDF/3TC is coformulated as a single-tablet regimen (STR). Clinical trial data have shown that this regimen is noninferior to efavirenz (EFV)- and darunavir/ritonavir (DRV/r)-based regimens.8,9 DOR compares
favorably to EFV and DRV/r in terms of side effects. DOR-based therapy has not been directly compared to INSTI-containing combinations for initial therapy. In patients starting their first ART regimen, treatment-emergent resistance to DOR has been observed.

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

Protease Inhibitor-Based Regimens as Initial Antiretroviral Therapy:

- Boosted atazanavir (ATV/c or ATV/r) plus ABC/3TC is no longer included in the list of Recommended Initial Regimens in Certain Clinical Situations because it has disadvantages when compared with other regimens in this category. In a randomized trial, ATV/r plus ABC/3TC was less potent than ATV/r plus TDF/FTC in people with HIV RNA >100,000 copies/mL. In a separate randomized trial, ATV/r was less well tolerated than DRV/r.

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

- DTG plus 3TC is now recommended by the Panel when ABC, TAF, or TDF cannot be used or are not optimal. This is based on the results of two large Phase 3 randomized clinical trials: DTG plus 3TC was noninferior to DTG plus TDF/FTC in terms of virologic efficacy, and no drug resistance was seen in either treatment group. Longer-term data are needed before this new two-drug regimen is recommended for most people with HIV.

- Other regimens that can be considered are DRV/r plus raltegravir (RAL), as long as a patient’s plasma HIV RNA is <100,000 copies/mL and CD4 cell count is >200/mm³, or DRV/r plus 3TC, although the data for this regimen are not as extensive as for other combinations.

- Lopinavir/ritonavir (LPV/r) plus 3TC is no longer recommended because of pill burden and poor tolerability.

Generic Antiretroviral Drugs:

- A growing number of generic ARV medications have been approved by the FDA since the last revision of these guidelines. In some situations, cost and access are among the factors to consider when choosing an ARV regimen (see Cost Considerations and Antiretroviral Therapy).
Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 1 of 2)

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order. Table 7 provides ARV recommendations based on specific clinical scenarios.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

<table>
<thead>
<tr>
<th>INSTI plus 2 NRTIs:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note:</strong> For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.</td>
</tr>
<tr>
<td>• BIC/TAF/FTC (AI)</td>
</tr>
<tr>
<td>• DTG/ABC/3TC (AI) if HLA-B*5701 negative</td>
</tr>
<tr>
<td>• DTG plus tenofovir/FTC (AI for both TAF/FTC and TDF/FTC)</td>
</tr>
<tr>
<td>• RAL plus tenofovir/FTC (BI for TDF/FTC, BII for TAF/FTC)</td>
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</table>

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

<table>
<thead>
<tr>
<th>INSTI plus 2 NRTIs:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note:</strong> For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.</td>
</tr>
<tr>
<td>• EVG/c/tenofovir/FTC (BI for both TAF/FTC and TDF/FTC)</td>
</tr>
<tr>
<td>• RAL plus ABC/3TC (CII) if HLA-B*5701 negative and HIV RNA &lt;100,000 copies/mL</td>
</tr>
</tbody>
</table>

Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

| (DRV/c or DRV/r) plus tenofovir/FTC (AI) |
| (ATV/c or ATV/r) plus tenofovir/FTC (BI) |
| (DRV/c or DRV/r) plus ABC/3TC (BII) if HLA-B*5701 negative (BII) |

NNRTI plus 2 NRTIs:

| DOR/TDF/3TC (BI) or DOR plus TAF/FTC (BI) |
| EFV plus TDF/FTC (BI for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, BII for EFV 600 mg plus TAF/FTC) |
| RPV/tenofovir/FTC (BI) if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm³ |

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

| DTG plus 3TC (BI) |
| DRV/r plus RAL BID (CI) if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm³ |
| DRV/r once daily plus 3TC (CI) |

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

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, BIC/TAF/FTC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/ABC/3TC, EFV 600 mg/TDF/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

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

TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

RAL can be given as RAL 400 mg BID or RAL 1200 mg (two, 600-mg tablets) once daily.
Table 6b. Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy

Pregnancy testing should be performed in those of childbearing potential prior to initiation of ART (AIII). Preliminary data suggest that there is an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception.6,7

Before Initiating DTG:

• Providers and people of childbearing potential should discuss the benefits and risks of using DTG, including the possible risk of NTDs; appropriate counseling should be provided so that the individual can make an informed decision about the use of this drug (AIII).

• DTG should not be prescribed for individuals:
  • Who are pregnant and within 12 weeks post-conception (AII); or
  • Who are of childbearing potential and planning to become pregnant (AII); or
  • Who are of childbearing potential, sexually active, and not using effective contraception (AIII).

• For those who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG use with the individual (BIII).

• It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect).

• The chemical structure of BIC is similar to DTG. There are no safety data on the use of BIC around the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART (AIII).

• In a person who is pregnant, BIC is not recommended because of insufficient safety data (AIII).

• In a person who is pregnant, EVG/c is also not recommended because low EVG concentrations have been reported when this drug is given during the second and third trimesters (AII).13

• Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States; however, data on RAL use during the first trimester is limited to fewer than 300 deliveries. As it is currently not known whether the association between DTG and NTDs represents a class effect, this potential risk should be discussed with people of childbearing potential who prefer an INSTI-containing regimen.

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

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

Key to Acronyms: ART = antiretroviral therapy; BIC = bictegravir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

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

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

The choice between an INSTI, PI, or NNRTI as the third drug in an initial ARV regimen should be guided by the regimen’s efficacy, barrier to resistance, adverse effects profile, convenience, comorbidities, concomitant
medications, and the potential for drug-drug interactions (see Tables 7 and 9 for guidance). The Panel’s Recommended Initial Regimens for Most People with HIV as listed in Table 6a include one of three INSTIs (BIC, DTG, or RAL) plus two NRTIs. For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI-containing regimens and INSTI-containing regimens, the INSTI was better tolerated and caused fewer treatment discontinuations.\textsuperscript{11,14,15}

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

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

NNRTI-based regimens (which include DOR, EFV, or rilpivirine [RPV]) may be optimal choices for some patients, although these drugs, especially EFV and RPV, have low barriers to resistance. The emergence of resistance at the time of virologic failure has been reported with DOR. EFV has a long track record of widespread use and is considered safe in persons of childbearing potential, and its minimal PK interaction with rifamycins makes it an attractive option for patients who require concomitant treatment for tuberculosis (TB). Most EFV-based regimens have excellent virologic efficacy, including in patients with high HIV RNA (except when EFV is used with ABC/3TC); however, the relatively high rate of central nervous system (CNS)-related side effects reduces the tolerability of EFV-based regimens. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA levels (>100,000 copies/mL) and low CD4 counts (<200 cells/mm\textsuperscript{3}). DOR is now approved for use in ART-naive individuals with HIV. It is available both as a single-drug pill to be used with two NRTIs and as part of an STR that also includes TDF/3TC. Both formulations are taken once daily without regard to food. In randomized trials, DOR was noninferior to both EFV and to DRV/r when either of these drugs were taken in combination with two NRTIs. DOR has CNS tolerability advantages over EFV and favorable lipid effects when compared
with both DRV/r and EFV. It also has fewer potential drug interactions than EFV or RPV, and, unlike RPV, virologic effects are not compromised in those with high HIV RNA levels and low CD4 cell counts.

In those patients who cannot safely be prescribed a combination regimen that contains two NRTIs, there are now several two-drug treatment options. DTG plus 3TC is an option when ABC, TAF, and TDF cannot be used or are not optimal. Two randomized trials that collectively enrolled >1,400 participants with baseline HIV RNA levels <500,000 copies/mL compared DTG plus 3TC to a three-drug regimen of DTG plus TDF/FTC. At week 48, DTG plus 3TC was noninferior to DTG plus TDF/FTC in terms of virologic efficacy. No treatment-emergent resistance was seen in either group. Another option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination can only be used in those with baseline CD4 cell counts >200 cells/mm³ and HIV RNA levels <100,000 copies/mL. A small, randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to DRV/r plus TDF/3TC, although this study has yet to be published.

Factors to Consider When Selecting an Initial Regimen

When selecting a regimen for an individual person with HIV, a number of patient- and regimen-specific characteristics should be considered. The goal is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen for the patient in order to achieve sustained virologic control. Some of the factors to consider during regimen selection can be grouped into the categories listed below. Table 7 includes recommendations for regimens to use in specific clinical scenarios.

Initial Characteristics to Consider in All Persons with HIV:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 count
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs.
- HLA-B*5701 status. Those who are positive should not receive ABC.
- Individual preferences
- Anticipated adherence to the regimen

Specific Comorbidities or Other Conditions:

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

Regimen-Specific Considerations:

- Regimen’s barrier to resistance
- Potential adverse effects
- Known or potential drug interactions with other medications (see Drug-Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of fixed-dose combination (FDC) formulations, food requirements)
- Cost and access (see Cost Considerations and Antiretroviral Therapy)
Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 1 of 4)

This table provides guidance to clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a person with HIV, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a person is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 9 for additional information regarding the advantages and disadvantages of particular ARV medications.

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

<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-ART Characteristics</strong></td>
<td>CD4 cell count &lt;200 cells/mm³</td>
<td><strong>Do Not Use the Following Regimens:</strong></td>
<td>A higher rate of virologic failure has been observed in those with low pretreatment CD4 cell counts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RPV-based regimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRV/r plus RAL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV RNA &gt;100,000 copies/mL</td>
<td><strong>Do Not Use the Following Regimens:</strong></td>
<td>Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RPV-based regimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ABC/3TC with EFV or ATV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRV/r plus RAL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA-B*5701 positive or result unknown</td>
<td>Do not use ABC-containing regimens.</td>
<td>ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.</td>
</tr>
<tr>
<td></td>
<td>ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when rapid initiation of ART is warranted</td>
<td>Avoid NNRTI-based regimens.</td>
<td>Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.</td>
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<td></td>
<td></td>
<td><strong>Avoid ABC.</strong></td>
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<td></td>
<td><strong>Recommended ART Regimens:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• (DRV/r or DRV/c) plus tenofoviri/FTC</td>
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<tr>
<td></td>
<td></td>
<td>• DTG plus tenofoviri/FTC</td>
<td></td>
</tr>
<tr>
<td><strong>ART-Specific Characteristics</strong></td>
<td>A 1-pill, once-daily regimen is desired</td>
<td><strong>STR Options as Initial ART Include:</strong></td>
<td>Do not use RPV-based regimens if HIV RNA is &gt;100,000 copies/mL and CD4 cell count is &lt;200/mm³.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BIC/TAF/3TC</td>
<td>Do not use DTG/ABC/3TC if patient is HLA-B*5701 positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DOR/TDF/3TC</td>
<td>Refer to Table 6b for further guidance before initiating DTG in persons of childbearing potential.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRV/c/TAF/FTC</td>
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<tr>
<td></td>
<td></td>
<td>• DTG/ABC/3TC</td>
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<td></td>
<td></td>
<td>• EFV/TDF/FTC</td>
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<td></td>
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<td>• EFV/TDF/3TC</td>
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<td>• EVG/c/TAF/FTC</td>
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<td>• EVG/c/TDF/FTC</td>
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<td></td>
<td>• RPV/TAF/FTC</td>
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<td></td>
<td></td>
<td>• RPV/TDF/FTC</td>
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<tr>
<td><strong>Food effects</strong></td>
<td>Regimens that Can be Taken Without Regard to Food:</td>
<td><strong>Regimens that Can be Taken Without Regard to Food:</strong></td>
<td>Oral bioavailability of these regimens is not significantly affected by food.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BIC-, DOR-, DTG-, or RAL-based regimens</td>
<td>Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.</td>
</tr>
</tbody>
</table>
### Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 2 of 4)

<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART-Specific Characteristics, continued</td>
<td>Food effects, continued</td>
<td>Regimens that Should be Taken with Food: • ATV/r- or ATV/c-based regimens • DRV/r- or DRV/c-based regimens • EVG/c/TAF/FTC&lt;sup&gt;a&lt;/sup&gt; • EVG/c/TDF/FTC&lt;sup&gt;a&lt;/sup&gt; • RPV-based regimens</td>
<td>Food improves absorption of these regimens. RPV-containing regimens should be taken with at least 390 calories of food.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Chronic kidney disease (defined as CrCl &lt;60 mL/min)</td>
<td>Avoid TDF unless the patient has ESRD. Use ABC or TAF. ABC may be used if patient is HLA-B&lt;sup&gt;*5701&lt;/sup&gt; negative. If HIV RNA &gt;100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). TAF may be used if CrCl &gt;30 mL/min. Consider avoiding ATV. ART Options When ABC, TAF or TDF Cannot be Used: • DTG plus 3TC • DRV/r plus 3TC • DRV/r plus RAL (if CD4 cell count &gt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt; and HIV RNA &lt;100,000 copies/mL)</td>
<td>TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 8 for specific dosing recommendations. TAF has less impact on renal function and lower rates of proteinuria than TDF. ATV has been associated with chronic kidney disease in some observational studies. ABC has not been associated with renal dysfunction. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.</td>
</tr>
<tr>
<td>Liver disease with cirrhosis</td>
<td>Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.</td>
<td></td>
<td>Refer to Appendix B, Table 8 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Avoid TDF. Use ABC or TAF. ABC may be used if patient is HLA-B&lt;sup&gt;*5701&lt;/sup&gt; negative. If HIV RNA &gt;100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).</td>
<td>TDF is associated with decreases in BMD along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF and ABC are associated with smaller declines in BMD than TDF.</td>
<td></td>
</tr>
<tr>
<td>Psychiatric illnesses</td>
<td>Consider avoiding EFV- and RPV-based regimens. Patients on INSTI-based regimens who have pre-existing psychiatric conditions should be closely monitored. Some ARVs are contraindicated and some psychiatric medications need dose adjustments when coadministered with certain ARVs.</td>
<td>EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series. See the drug-drug interaction tables (Tables 19a, 19b, and 19d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.</td>
<td></td>
</tr>
<tr>
<td>Patient or Regimen Characteristics</td>
<td>Clinical Scenario</td>
<td>Consideration(s)</td>
<td>Rationale/Comments</td>
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</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>HAD</td>
<td>Avoid EFV-based regimens if possible. Favor DTG- or DRV-based regimens.</td>
<td>EFV-related neuropsychiatric effects may confound assessment of ART’s beneficial effects on improvement of HAD-related symptoms. There is a theoretical CNS penetration advantage of DTG- or DRV-based regimens.</td>
</tr>
<tr>
<td>Medication-assisted treatment for opioid dependence</td>
<td>Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring is recommended, as medications used to treat opioid dependence may need to be adjusted in some patients.</td>
<td>EFV reduces methadone concentrations and may lead to withdrawal symptoms. See the drug-drug interaction tables (Tables 19a, 19b, and 19d) for dosing recommendations.</td>
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</tr>
<tr>
<td>High cardiac risk</td>
<td>Consider avoiding ABC- and LPV/r-based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen. BIC-, DOR-, DTG-, RAL-, or RPV-based regimens may be considered for those with high cardiac risk.</td>
<td>An increased CV risk with ABC has been observed in some studies. Observational cohort studies reported an association between some PIs (DRV, IDV, FPV, and LPV/r) and an increased risk of CV events; this risk has not been seen with ATV (see text). Further study is needed. BIC-, DOR-, DTG-, RAL- or RPV-based regimens have more favorable lipid profiles than other regimens, although evidence on whether this improves CV outcomes is lacking. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.</td>
<td></td>
</tr>
<tr>
<td>Cardiac QTc interval prolongation</td>
<td>Consider avoiding EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.</td>
<td>High EFV or RPV concentrations may cause QT prolongation.</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>The Following ARV Drugs Have Been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c BIC, DOR, DTG, RAL, and RPV have fewer lipid effects.</td>
<td>TDF has been associated with lower lipid levels than ABC or TAF. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.</td>
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</tr>
<tr>
<td>Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care</td>
<td>Consider using regimens with a boosted PI or DTG. BIC also has a high barrier to resistance, but there is currently no data on its efficacy in this population.</td>
<td>These regimens have a high genetic barrier to resistance. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.</td>
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</tr>
<tr>
<td>Patient or Regimen Characteristics</td>
<td>Clinical Scenario</td>
<td>Consideration(s)</td>
<td>Rationale/Comments</td>
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<tr>
<td><strong>Presence of Other Conditions, continued</strong></td>
<td><strong>Pregnancy</strong></td>
<td>Until more information is available, do not initiate a DTG-based regimen for those who are pregnant and within 12 weeks post-conception, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.⁶,⁷ Refer to Table 6b and the Perinatal Guidelines for further guidance on ARV use during pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Patients of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception</strong></td>
<td>Until more information is available, do not initiate a DTG-based regimen in these patients, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.⁶,⁷ Refer to Table 6b for further guidance before initiating an INSTI.</td>
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<tr>
<td><strong>Presence of Coinfections</strong></td>
<td><strong>HBV infection</strong></td>
<td>Use TDF or TAF, with FTC or 3TC, whenever possible. If TDF and TAF Are Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).</td>
<td>TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug that is active against HBV.</td>
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<td></td>
<td><strong>HCV treatment required</strong></td>
<td>Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.</td>
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<tr>
<td></td>
<td><strong>Treating TB disease with rifamycins</strong></td>
<td>TAF and BIC are not recommended with any rifamycin-containing regimen. If Rifampin is Used: • The following are not recommended: PI/c or PI/r, BIC, EVG, DOR, RPV, or TAF: • EFV can be used without dose adjustment. • If RAL is used, increase RAL dose to 800 mg BID. Do not use once-daily RAL. • Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label).</td>
<td>Rifamycins may significantly reduce TAF and BIC exposures. Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, DOR, and RPV. Rifampin has a less significant effect on EFV concentration than on the concentrations of other NNRTIs, PIs, and INSTIs. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. See the drug-drug interaction tables (Tables 19a, 19b, 19c, 19d and 19e) and TB/HIV Coinfection for information on ARV use with rifamycins.</td>
</tr>
</tbody>
</table>

* TAF and TDF are two approved forms of tenofovir. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BID = twice daily; BMD = bone mineral density; COBI = cobicistat; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FTC = emtricitabine; HAD = HIV-associated dementia; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase
Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>ABC/3TC</th>
<th>TAF/FTC</th>
<th>TDF/FTC</th>
<th>TDF/3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Available Coformulations for ART-Naive Patients</strong></td>
<td>• ABC/3TC</td>
<td>• TAF 25 mg/FTC</td>
<td>• TDF/FTC</td>
<td>• TDF/3TC</td>
</tr>
<tr>
<td></td>
<td>• DTG/ABC/3TC</td>
<td>• BIC/TAF 25 mg/FTC</td>
<td>• EFV/TDF/FTC</td>
<td>• DOR/TDF/3TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRV/c/TAF 10 mg/FTC</td>
<td>• EVG/c/TDF/FTC</td>
<td>• EFV 600 mg/TDF/3TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EVG/c/TAF 10 mg/FTC</td>
<td>• RPV/TDF/FTC</td>
<td>• EFV 400 mg/TDF/3TC</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>ABC:</td>
<td>TAF:</td>
<td>TDF:</td>
<td>TDF:</td>
</tr>
<tr>
<td></td>
<td>• HSR to ABC is associated with the presence of HLA-B*5701 allele</td>
<td>• Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF)</td>
<td>• Renal insufficiency, proximal renal tubulopathy</td>
<td>• Renal insufficiency, proximal renal tubulopathy</td>
</tr>
<tr>
<td></td>
<td>• Increase in CV events is associated with ABC use in some, but not all, cohort studies</td>
<td>• Decrease in BMD (less than with TDF; similar to ABC)</td>
<td>• Decrease in BMD</td>
<td>• Decrease in BMD</td>
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<tr>
<td><strong>Other Considerations</strong></td>
<td>• Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to allergy list</td>
<td>Also used for HBV treatment. Discontinuation may precipitate flare of HBV.</td>
<td>See Appendix B, Table 8 for dose recommendations in patients with renal insufficiency.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If HIV RNA &gt;100,000 copies/mL, use only with DTG</td>
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</tbody>
</table>

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
Summary

FDA-approved NRTIs include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), ABC, TDF, TAF, 3TC, and FTC. Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States due to high rates of serious toxicities, including bone marrow suppression from ZDV use. Other toxicities that mainly occur due to mitochondrial toxicity may lead to myopathy, peripheral neuropathy, hepatic steatosis, lactic acidosis, and lipoatrophy. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.26,27

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended for use as components of initial therapy. Table 6a provides recommendations and ratings for the individual regimens. These recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs. TAF and TDF are two approved forms of tenofovir. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.28 TAF is less likely to cause kidney and bone toxicities than TDF. TDF is associated with lower lipid levels than TAF. Safety, cost, and access are among the factors to consider when choosing between these drugs. ABC/3TC and TDF/3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug10,29,30 (see also the discussion in the DTG section).31

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each was used in combination with either EFV or ATV/r. In patients with baseline HIV RNA ≥100,000 copies/mL, there was a significantly shorter time to virologic failure with ABC/3TC than with TDF/FTC regardless of whether the third active drug was EFV or ATV/r.10 In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. Virologic efficacy was similar in the two study arms, including in a subgroup with HIV RNA ≥100,000 copies/mL.30

- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701–negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. At week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants than among TDF/FTC-treated participants.29

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

- Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of EVG/c/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.
  - TAF/FTC was virologically noninferior to TDF/FTC at week 48 (92% vs. 90% of participants achieved plasma HIV RNA <50 copies/mL, respectively),32 but TAF/FTC was superior to TDF/FTC at week 144 (84.2% vs. 80%), largely driven by a higher rate of treatment discontinuation in the TDF arm.33
  - Participants in the TAF arm had significantly smaller reductions in BMD at the spine and hip than those in the TDF arm through 144 weeks.33 They also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through week 96.34 Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at 96 weeks, with no change in total cholesterol to HDL ratio.35
• Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC each administered in combination with boosted DRV in ART-naive subjects:
  • A Phase 2 study of coformulated DRV/c plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% vs. 74%) in treatment-naive patients.36 In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.
  • The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At 48 weeks, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.37
• One analysis evaluated data from 11 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF or TAF when either drug was taken with or without PK boosters (RTV or COBI). There were no significant differences between unboosted TDF and TAF in terms of virologic efficacy or in the number of participants who discontinued treatment due to renal or bone adverse events or fractures. However, bone- and renal-related toxicities were more pronounced when TDF was used in combination with RTV or COBI.28
• To assess the ability of TAF to maintain HIV and HBV suppression, 72 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 log10 IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.38 In this study, 96% of participants were on a TDF/FTC-containing regimen prior to the switch. Key results of the study showed that:
  • Those who switched to EVG/c/TAF/FTC maintained HIV suppression: 94.4% and 91.7% of participants at 24 and 48 weeks, respectively. At 24 and 48 weeks, 86.1% and 91.7% of participants had HBV DNA <29 log10 IU/mL.
  • Decreases in markers of proximal tubular proteinuria and biomarkers of bone turnover were seen in those who switched to EVG/c/TAF/FTC.38

**Dual-Nucleoside Reverse Transcriptase Inhibitor Choices** (In alphabetical order)

**Abacavir/Lamivudine (ABC/3TC)**

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.31,39-41

**Adverse Effects**

**Hypersensitivity Reactions:**

• Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50% of HLA-B*5701–positive patients will have an ABC-related HSR if given this drug.42,43 HLA-B*5701 testing should be done if the use of ABC is being considered. In a patient who tests positive for HLA-B*5701, ABC should not be given and ABC hypersensitivity should be noted on the allergy list. Patients who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR should never be rechallenged, regardless of their HLA-B*5701 status.

**Cardiovascular Risk:**

• An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.19,44
Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association. Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.

An analysis of data from NA-ACCORD found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.

No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations:

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- ABC and 3TC are available separately and as a coformulated tablet in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in patients with renal dysfunction.

The Panel’s Recommendations:

- ABC should only be prescribed for patients who are HLA-B*5701 negative.
- On the basis of clinical trial safety and efficacy data, experience in clinical practice, and the availability of DTG/ABC/3TC as an FDC, the Panel classifies DTG/ABC/3TC as a Recommended Initial Regimen for Most People with HIV (AI) (see the discussion of DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, ATV/c, DRV/c, DRV/r, or RAL is only recommended for patients with pretreatment HIV RNA levels <100,000 copies/mL. See Table 6a for more detailed recommendations on the use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

TAF, an oral prodrug of tenofovir (TFV), is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

Adverse Effects

Renal and Bone Effects:

- The potential for adverse kidney and bone effects is lower with TAF than with TDF. In randomized controlled trials that compared TAF and TDF in treatment-naive or virologically suppressed patients, TAF had more favorable effects on renal biomarkers and bone density than TDF (described below).

Lipid Effects:

- In randomized controlled trials in ART-naive patients, as well as in switch studies (described below), levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and TDF. The clinical significance of this finding is not clear.

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV
Other Factors and Considerations:

- TAF/FTC is available in FDCs with DRV/c, EVG/c or RPV, allowing the regimens to be administered as a single pill taken once daily with food.

- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see the INSTI section below).

- TAF-containing regimens are approved for patients with eGFR ≥30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in patients on hemodialysis with eGFRs <15 mL/min.59

- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).38

The Panel’s Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data, and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with BIC, DTG, and RAL.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) and Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC)

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.61,62-70 In a 10-day, open-label, randomized monotherapy trial that was not powered to find a difference between the arms, FTC 200 mg once daily demonstrated a viral load reduction of 1.7 log10 from baseline, compared with a reduction of 1.5 log10 from baseline for 3TC 150 mg twice daily.71 In a meta-analysis of 12 trials, no significant difference in treatment success was found between 3TC and FTC.72 In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with an NNRTI (EFV or NVP)53 or with a boosted PI.74 TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis; however, it is worth noting that the people in this cohort who were taking 3TC generally had higher viral loads, lower CD4 cell counts, and were more likely to be using injection drugs at the start of the study than people who were taking FTC.73 There was no difference in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI.74 A retrospective analysis of an Italian national database found that viral resistance was more common with TDF/3TC than with TDF/FTC, but this was not observed in clinical trials.75

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.76,77 Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)78 and pre-existing renal impairment.79 Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that there is a greater risk of renal dysfunction when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.77,79-83

- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC with PK boosting.28
Bone Effects:

- While initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants. BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above).

- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.

- Adverse bone outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that fractures and discontinuation due to bone adverse events occur more frequently among patients who take TDF/FTC with PK boosting.

Other Factors and Considerations:

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.

- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 mg.

- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring). In patients who have pre-existing renal insufficiency (creatinine clearance [CrCl] <60 mL/min), use of TDF should generally be avoided. If TDF is used, a dose adjustment is required if the patient’s CrCl falls below 50 mL/min (see Appendix B, Table 8 for dose recommendations).

- TDF, FTC, and 3TC are active against HBV. In patients with HIV/HBV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).

The Panel’s Recommendations:

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination’s availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most persons with HIV when combined with DTG or RAL. See Table 6a for recommendations regarding use of TDF/FTC with other drugs.

- TDF should be used with caution or avoided in patients with renal disease and osteoporosis.

- Specific attention should be given to renal and bone safety monitoring when TDF is used, especially with PK boosters. Boosters should be avoided when possible in patients taking TDF.
## Integrase Strand Transfer Inhibitor–Based Regimens

### Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy-Naive Patients

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>BIC</th>
<th>DTG</th>
<th>EVG</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
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<td></td>
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<tr>
<td>Once daily</td>
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<tr>
<td>Twice Daily</td>
<td></td>
<td></td>
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<tr>
<td>In ART-naive or INSTI-naive persons</td>
<td>Once Daily:</td>
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<tr>
<td>If used with certain CYP3A4 and UGT1A1 inducers; or</td>
<td></td>
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<tr>
<td>In INSTI-experienced persons with certain INSTI DRMs</td>
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<tr>
<td>400 mg BID, or</td>
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<td>1200 mg (two 600-mg tablets) once daily</td>
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<td><strong>STR Available for ART-Naive Patients</strong></td>
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<tr>
<td>BIC/TAF/FTC</td>
<td>DTG/ABC/3TC</td>
<td>• EVG/c/TAF/FTC</td>
<td>• EVG/c/TDF/FTC</td>
<td>No</td>
</tr>
<tr>
<td><strong>Available as a Single-Drug Tablet</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Approved for ART-Experienced Patients</strong></td>
<td>No</td>
<td>Yes, with BID dosing for patients with some INSTI DRMs</td>
<td>No</td>
<td>Yes, for patients with DRM to PI/r or NNRTIs, but no DRM to INSTIs</td>
</tr>
<tr>
<td><strong>Virologic Efficacy Against EVG- or RAL-Resistant HIV</strong></td>
<td>In vitro data indicate activity, but no clinical trial data are available</td>
<td>Yes, for some isolates; effective with 50 mg BID dose</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td></td>
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<tr>
<td>Nausea, diarrhea (GI disturbance greater with EVG/c), headache, insomnia. Depression and suicidality are rare, occurring primarily in patients with pre-existing psychiatric conditions.</td>
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<tr>
<td>↑ CPK (4%)</td>
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<td></td>
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<tr>
<td>Hypersensitivity, hepatotoxicity, ↑ CPK, myositis</td>
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<tr>
<td>↑ TG, ↑ LDL</td>
<td></td>
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<tr>
<td>↑ CPK, myopathy, hypersensitivity, SJS/TEN</td>
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<tr>
<td><strong>CYP3A4 Drug-Drug Interactions</strong></td>
<td>CYP3A4 substrate</td>
<td>CYP3A4 substrate (minor)</td>
<td>EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor</td>
<td>No</td>
</tr>
<tr>
<td><strong>Chelation with Polyvalent Cation Supplements and Antacids</strong></td>
<td>Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 19d for recommendations regarding dosing separation of INSTIs and these drugs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other Key Potential Drug Interactions</strong></td>
<td>UGT1A1 substrate, OAT1 and MATE2 inhibitor</td>
<td>p-gp substrate, UGT1A1 substrate</td>
<td>EVG is a UGT1A1 substrate; COBI is a p-gp inhibitor</td>
<td>UGT1A1 substrate</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DRM = drug resistance mutation; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; INSTI = integrase strand transfer inhibitor; LDL = low density lipoprotein; MATE = multidrug and toxic compound extrusion; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; OAT = organic anionic transporter; p-gp = p-glycoprotein; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; SJS/TEN = Stevens Johnson Syndrome/toxic epidermal necrolysis; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; UGT = uridine diphosphate glucuronosyltransferase.
Summary

Four INSTIs—BIC, DTG, EVG, and RAL—are approved for use in ART-naive patients with HIV. All INSTIs are generally well tolerated, though there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have rarely been reported in patients receiving INSTI-based regimens. BIC, DTG, and EVG are available as components of STRs—BIC is coformulated with TAF/FTC, DTG is coformulated with ABC/3TC, and EVG is coformulated with a PK enhancer (COBI) and either TAF/FTC or TDF/FTC. The Panel classifies the three unboosted INSTI-based regimens (BIC, DTG, and RAL) as Recommended Initial Regimens for Most People with HIV. Among the INSTI-based regimens, RAL-containing regimens have the longest clinical experience, and they have been shown to have durable virologic efficacy; however, they have a higher pill burden than BIC- and DTG-containing regimens. EVG and RAL have lower barriers to resistance than BIC and DTG. In clinical trials of ART-naive patients who received BIC or DTG plus two NRTIs, resistance was not seen at virologic failure. Because of its high barrier to resistance, DTG may be considered for patients who must start ART before resistance test results are available (e.g., during acute HIV infection and in the setting of certain opportunistic infections). EVG-based regimens are now considered Recommended Initial Regimens in Certain Clinical Situations, because they require boosting with COBI, which results in a greater potential for interaction with concomitant medications.

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

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

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen for Most People with HIV

Bictegravir (BIC)

BIC is an INSTI that is approved by the FDA for initial therapy in adults with HIV as a component of a single-tablet, once-daily regimen with TAF and FTC.

Efficacy in Clinical Trials:

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at week 48.
- The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At week 48, 89% of participants in the BIC arm and 93% of those in the DTG arm achieved HIV RNA <50 copies/mL ($P = 0.12$).
- The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At week 48, 92.4% of participants in the BIC/TAF/FTC arm and 93% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL ($P = 0.78$).

Adverse Effects:

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

- BIC is a CYP3A4 substrate and a UGT1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John’s wort should also be avoided.88

- BIC is an inhibitor of the drug transporters OAT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is contraindicated with BIC/TAF/FTC.

- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, it is unlikely to affect the metabolism of medications that are CYP3A4 substrates.

- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids, or calcium or iron supplements). See Table 19d for dosing recommendations when using BIC with these products.

- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are typically observed within the first 4 weeks (with a median increase of 0.10 mg/dL after 48 weeks). This effect on creatinine secretion is similar to that seen with other medications used in people with HIV, including DTG and COBI.

- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations, and BIC should not be used in these individuals until more data are available.

- BIC and DTG share a similar chemical structure. It is unclear whether DTG is the only INSTI with the potential to cause NTDs or if other INSTIs also carry this risk.

The Panel’s Recommendation:

- On the basis of clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a Recommended Initial Regimen for Most People with HIV (AI).

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

Dolutegravir (DTG)

DTG is an INSTI with a higher barrier to resistance than EVG or RAL. In ART-naive patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. It is given once daily, with or without food. Preliminary data from Botswana suggest that there may be an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception.6,7 More detailed discussions of this potential risk and recommendations for the use of this drug are found below and in Table 6b.

Efficacy in Clinical Trials

The efficacy of DTG in ART-naive patients has been evaluated in several fully powered randomized controlled clinical trials. In these five trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.
DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have shown virologic efficacy that is similar to BIC/TAF/FTC (see the discussion in the BIC section above).4,5
- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily. Each drug was administered in combination with an investigator-selected, two-NRTI regimen (either ABC/3TC or TDF/FTC) to 822 participants. At week 96, DTG was noninferior to RAL.70

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

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

DTG plus Two NRTIs versus PI/r plus Two NRTIs:

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to DRV/r 800 mg/100 mg once daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 48, DTG was superior to DRV/r because of the higher rate of discontinuation in the DRV/r arm.90 The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pretreatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.91
- The ARIA trial, an open-label, Phase 3b randomized controlled trial, compared the efficacy and safety of DTG/ABC/3TC to ATV/r plus TDF/FTC in ART-naive, nonpregnant women. At week 48, 82% of participants in the DTG group achieved HIV RNA viral loads <50 copies/mL compared with 71% in the ATV group (P = 0.005). The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.92

DTG plus Two NRTIs versus DTG plus 3TC:

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

Adverse Effects:

- DTG is generally well tolerated. The most commonly reported adverse reactions of moderate-to-severe intensity were insomnia and headache.
- Case series of neuropsychiatric adverse events (sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.93,94 Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs.95,96 However, analyses of data from large randomized controlled trials as well as a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and other ARV regimens,97 with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs,98 not just DTG. Further studies will be needed to clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric...
adverse events has not been defined.

- Preliminary data from an observational surveillance study of birth outcomes among pregnant women on ART in Botswana identified NTDs in four infants born to 596 women (0.67%) who initiated a DTG-based regimen prior to pregnancy, and who were still receiving it at the time of conception. The incidence of NTDs among infants born to women who were receiving other ARV drugs at the time of conception was 0.1%. This study is ongoing, and more data from births among women who were using a DTG-based regimen around the time of conception are expected. See Table 6b for recommendations on prescribing INSTIs as part of initial therapy.

Other Factors and Considerations:

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment (mean increase in serum creatinine was 0.11 mg/dL after 48 weeks).

- DTG has fewer drug interactions than EVG/c. See Drug-Drug Interactions for specific drug-drug interactions that require dosage adjustment.

- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see Drug-Drug Interactions). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.

- Treatment-emergent mutations that confer DTG resistance have not been reported in patients receiving DTG as part of a three-drug regimen for initial therapy, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel’s Recommendations:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC (AI), TAF/FTC (AI), or TDF/FTC (AI) as a Recommended Initial Regimen for Most People with HIV.

- A pregnancy test should be performed for those of childbearing potential prior to initiation of DTG (AIII).

- For those of childbearing potential who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG with the individual (BIII).

- Until more information is available, DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception (AII), or
  - Who are of childbearing potential and who are planning to become pregnant (AII) or who are sexually active and not using effective contraception (AIII).

Raltegravir (RAL)

RAL was the first INSTI approved for use in both ARV-naive and ARV-experienced patients.

Efficacy in Clinical Trials

**RAL 400 mg Twice Daily plus Two NRTIs versus Comparator Drug plus Two NRTIs:**

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label, randomized trial.

  - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in
combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.\textsuperscript{66} RAL was superior to EFV at 4 and 5 years,\textsuperscript{69,99} in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.

- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.

- The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads $\geq 100,000$ copies/mL and 125 participants with baseline viral loads $<100,000$ copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, there was no difference in virologic response between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.\textsuperscript{70}

- ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the PI/r arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.\textsuperscript{11}

**RAL 1,200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:**

- In a Phase 3, randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1,200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each administered with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 cell count.\textsuperscript{100}

**Adverse Effects:**

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.

- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.\textsuperscript{101}

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

**Other Factors and Considerations:**

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients.

- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids is not recommended. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See Table 19d for dosing recommendations.

- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.

**The Panel’s Recommendations:**

- On the basis of these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets)
once daily or as 400 mg twice daily plus TDF/FTC (BI) or TAF/FTC (BII) as a Recommended Initial Regimen for Most People with HIV.

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

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen in Certain Clinical Situations

Elvitegravir (EVG)

EVG is available as a component of two STRs: EVG/c/TDF/FTC and EVG/c/TAF/FTC. COBI is a specific, potent CYP3A inhibitor that has no activity against HIV. It acts as a PK enhancer of EVG, which allows for once-daily dosing of the combination but increases the likelihood of significant drug interactions.

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ART-naive participants has been evaluated in two randomized, double-blind active-controlled trials.
  - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.\(^\text{103}\)
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.\(^\text{104}\)
  - In a randomized, blinded trial performed in women with HIV, EVG/c/TDF/FTC had superior efficacy when compared to ATV/r plus TDF/FTC, in part because of a lower rate of treatment discontinuation.\(^\text{15}\)
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR \(\geq 50\) mL/min.\(^\text{32,35}\)
  - At 48 and 96 weeks, TAF was noninferior to TDF when both drugs were combined with EVG/c/FTC; at 144 weeks, EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC.\(^\text{33}\)

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.\(^\text{103,104}\)
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.\(^\text{105}\)
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see the discussion under DTG).

Other Factors and Considerations:

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see Drug-Drug Interactions).\(^\text{106}\)
- Administering EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see Drug-Drug Interactions). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG dosing.
• COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.\textsuperscript{107} Patients with a confirmed increase in serum creatinine \textgreater 0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be closely monitored and evaluated for evidence of TDF-related proximal renal tubulopathy.\textsuperscript{83}

• EVG/c/TDF/FTC \textbf{is not recommended} for patients with pretreatment estimated CrCl \textless 70 mL/min.\textsuperscript{83}

• EVG/c/TAF/FTC \textbf{is not recommended} for patients with pretreatment estimated CrCl \textless 30 mL/min.

• At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.\textsuperscript{103,104} These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.

The Panel’s Recommendation:

• On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as \textbf{Recommended Initial Regimens in Certain Clinical Situations (B1)}. EVG/c/TAF/FTC should only be used in people with estimated CrCl \geq 30 mL/min; EVG/c/TDF/FTC should only be used in people with estimated CrCl \geq 70 mL/min.

\section*{Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens}

\textbf{Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors that are Recommended for Antiretroviral Therapy-Naive Patients}

<table>
<thead>
<tr>
<th></th>
<th>DOR</th>
<th>EFV</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Food Requirement</strong></td>
<td>With or without food</td>
<td>On an empty stomach</td>
<td>With a meal</td>
</tr>
<tr>
<td><strong>STR Available for ART-Naive Patients</strong></td>
<td>• DOR/TDF/3TC</td>
<td>• EFV 600 mg/TDF/FTC</td>
<td>• RPV/TAF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EFV 600 mg/TDF/3TC</td>
<td>• RPV/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EFV 400 mg/TDF/3TC</td>
<td></td>
</tr>
<tr>
<td><strong>Available as a Single-Drug Tablet</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Generally well tolerated</td>
<td>• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, somnolence, and insomnia</td>
<td>• Depression, headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Skin rash</td>
<td>• Skin rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• QT prolongation</td>
</tr>
<tr>
<td><strong>CYP3A4 Drug-Drug Interactions</strong></td>
<td>CYP3A4 substrate</td>
<td>CYP3A4 substrate, mixed inducer/inhibitor</td>
<td>CYP3A4 substrate</td>
</tr>
<tr>
<td><strong>Other Significant Drug Interactions</strong></td>
<td>None</td>
<td>CYP2B6 and 2C19 inducer</td>
<td>RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug-Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids.</td>
</tr>
</tbody>
</table>

\textbf{Key to Acronyms:} 3TC = lamivudine; CNS = central nervous system; CYP = cytochrome P; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
**Summary**

Five NNRTIs (delavirdine [DLV], DOR, EFV, etravirine [ETR], nevirapine [NVP], and RPV) are currently approved by the FDA for the treatment of HIV when used in combination with other ARV drugs.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) are the prevalence of NNRTI-resistant viral strains in ART-naive patients\textsuperscript{108} and the drugs’ low barrier for the development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see Drug-Resistance Testing). High-level resistance to all NNRTIs (except ETR or DOR) may occur with a single mutation. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.\textsuperscript{109,110} DOR-, EFV-, and RPV-based regimens are now categorized as Recommended Initial Regimens in Certain Clinical Situations for ART-naive patients.

**Doravirine (DOR)**

**Efficacy in Clinical Trials**

The efficacy of DOR-based therapy for treatment of HIV in ART-naive individuals was demonstrated in two randomized, double-blind, placebo-controlled trials.

**DOR-Based Regimen versus EFV-Based Regimen:**

- In DRIVE-AHEAD, 734 participants received either DOR/TDF/3TC or EFV/TDF/FTC, both as STRs.\textsuperscript{9}
  - At 48 weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, with 84.3% of participants who received DOR/TDF/3TC and 80.8% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Virologic responses overall were lower in participants with pre-ART HIV RNA >100,000 copies/mL, but there was no difference between the DOR and EFV groups.
  - A greater proportion of participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.3% vs. 2.7%). Neuropsychiatric side effects were more common in the EFV arm.
  - Genotype resistance results were reported for 13 participants with virologic failure in the DOR arm and 10 participants in the EFV arm. For the DOR arm, seven out of 13 participants had NNRTI resistance and five out of 13 had NRTI resistance; for EFV, nine out of 10 participants had NNRTI resistance and five out of 10 had NRTI resistance.
  - The DOR group had no change in LDL cholesterol and non-HDL cholesterol among participants, whereas both LDL and non-HDL cholesterol increased with EFV use.
  - At week 96, 77.5% and 73.6% of participants in the DOR arm and the EFV arm had maintained HIV RNA <50 copies/mL, respectively.\textsuperscript{111}

**DOR-Based Regimen versus DRV/r-Based Regimen:**

- In DRIVE-FORWARD, 769 participants received DOR or DRV/r once daily along with two investigator-selected NRTIs, either ABC/3TC or TDF/FTC.\textsuperscript{8}
  - At 48 weeks, DOR was found to be noninferior to DRV/r when these drugs were administered with two NRTIs. Eighty-four percent of study participants receiving DOR achieved HIV RNA <50 copies/mL at 48 weeks, compared to 80% of participants receiving DRV/r.
  - Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.
  - At week 96, DOR was superior to DRV/r in terms of virologic suppression,\textsuperscript{112} there was a higher rate of discontinuation in the DRV/r group.
• Genotype resistance results were reported for seven and eight participants with virologic failure in the DOR and DRV/r arms, respectively. No drug resistance mutations were detected in either group.

• Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol and triglycerides were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations:
• DOR is available as a single-drug, 100-mg tablet and as part of an STR that contains DOR/TDF/FTC 100 mg/300 mg/300 mg, and is dosed once daily, with or without food.

• DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 19b).

• DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.

• Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.

• DOR-based regimens have not been directly compared to INSTI-based regimens in clinical trials.

• There are currently no data on the safety of DOR use during pregnancy.

The Panel’s Recommendations:
• On the basis of the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC (BI) and DOR plus two NRTIs (BI for TDF/FTC and BIII for TAF/FTC) as Recommended Initial Regimens in Certain Clinical Situations.

• Because the number of participants who received DOR plus ABC/3TC is much lower than the number who received TDF/FTC plus DOR, the Panel considers ABC/3TC plus DOR to be an option for initial therapy, but the Panel has less confidence in this regimen than in the other DOR-containing regimens listed above (CI).

Efavirenz (EFV)
Efficacy in Clinical Trials:
• Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. In clinical trials, EFV-based regimens have demonstrated superiority or noninferiority to several comparator regimens in ART-naive patients.

• In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.

• In the ECHO and THRIVE studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.

• In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.

• The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 48
weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.

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

- In the SINGLE trial, a DTG-based regimen was superior to EFV at the primary endpoint of viral suppression at week 48.31
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks,66 but RAL was superior to EFV at 4 and 5 years,69,99 in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label STaR trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.118

ENCORE 1 (a multinational, randomized, placebo-controlled trial) compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg (reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.119 While the frequency of overall adverse events was not different between groups, EFV-related adverse events occurred less frequently in the EFV 400 mg group than in the EFV 600 mg group. Although there were fewer self-reported CNS events in the 400 mg group, the groups had similar rates of psychiatric events. The 400-mg dose of EFV is now approved in the United States for initial treatment of HIV infection and is coformulated with TDF and 3TC in an FDC tablet. However, long-term experience and clinical efficacy data regarding its use during pregnancy and in patients with TB/HIV coinfecrion are lacking.

Adverse Effects:

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use has also been associated with suicidality; however, various large studies have provided different results. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (LPV/r, ATV, ATV/r, or ABC-based regimens).120 Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behavior among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses.121 This association, however, was not found in analyses of three large observational cohorts,122,123 or in a retrospective cohort study that used U.S. administrative pharmacy claims data.124 A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried an increased risk of suicidal ideation or depression compared to NVP.125
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.126,127 Consider an alternative therapy to EFV in patients taking medications known to increase the risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.

Other Factors and Considerations:

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.
• EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily STR tablet that uses 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children who weigh ≥35 kg.\(^{128,129}\)

• EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6; therefore, it may potentially interact with other drugs that use the same pathways (see Tables 19b, 20a, and 20b).

• EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.\(^{130}\) A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).\(^{131}\)

• Screening for depression and suicidality is recommended for people with HIV who are taking a regimen that includes EFV.

The Panel’s Recommendations:

• Given the availability of regimens with fewer treatment-limiting adverse events and also with noninferior or superior efficacy, the Panel classifies EFV/TDF/FTC or EFV/TDF/3TC (BI) or EFV plus TAF/FTC (BII) as Recommended Initial Regimens in Certain Clinical Situations.

• Randomized clinical trial data have demonstrated the efficacy of lower-dose (400 mg) EFV,\(^{119}\) but this dose has not been studied in a U.S. population, in pregnant women, or in patients with TB/HIV coinfection. The Panel therefore classifies the use of reduced-dose EFV as a Recommended Initial Regimen in Certain Clinical Situations (CI).

Rilpivirine (RPV)

RPV is an NNRTI that is approved for use in combination with NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL.

Efficacy in Clinical Trials:

• Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.\(^{117}\) At 96 weeks, the following findings were reported:
  • RPV was noninferior to EFV overall.
  • Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with virologic failure, NNRTI and NRTI resistance was more frequently identified in those treated with RPV.
  • Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 cell counts <200 cells/mm\(^3\) than in those with CD4 cell counts ≥200 cells/mm\(^3\).
  • STaR, a Phase 3b, open-label study, compared the FDC of RPV/TDF/FTC and EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks\(^ {132}\) were similar to the findings reported at 48 weeks.\(^ {118}\)
    • RPV was noninferior to EFV overall.
    • RPV was superior to EFV in patients with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among patients with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated patients than in EFV-treated patients.
    • There were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% vs. 1%, respectively).
  • The FDC tablet of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence

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

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019
study. In this study, participants taking the coformulated drug had plasma concentrations of RPV, FTC, and TAF 25 mg that were similar to concentrations seen in participants who received RPV as the single-drug tablet and TAF/FTC when given as part of the FDC of EVG/c/TAF 10 mg/FTC.\textsuperscript{60}

**Adverse Effects:**

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer patients in the RPV arms discontinued therapy due to adverse events. However, up to 9\% of clinical trial participants experienced depressive disorders, including approximately 1\% of participants who had suicidal thoughts or who attempted suicide. Patients with severe depressive symptoms should be evaluated to assess whether symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

**Other Factors and Considerations:**

- RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC and with TDF/FTC. Among available STRs, RPV/TAF/FTC is the smallest tablet.

- RPV/TAF/FTC and RPV/TDF/FTC are given once daily and must be administered with a meal (containing at least 390 kcal).

- **RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for persons with HIV who have achieved viral suppression.\textsuperscript{133} However, this combination has not been studied in ART-naive individuals, and it is not recommended for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).**

- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is contraindicated in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see Drug-Drug Interactions for dosing recommendations).

- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug-Drug Interactions).

- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

**The Panel’s Recommendations:**

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as Recommended Initial Regimens in Certain Clinical Situations.

- Use of RPV with TAF/FTC (BII) or TDF/FTC (BI) should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 cell counts >200 cells/mm\textsuperscript{3}.

- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.
Protease Inhibitor-Based Regimens

Table 8d. Characteristics of Protease Inhibitor Options that are Recommended for Antiretroviral Therapy-Naive Patients

<table>
<thead>
<tr>
<th></th>
<th>ATV</th>
<th>DRV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>Once daily</td>
<td>• Once daily for PI-naive patients</td>
</tr>
<tr>
<td></td>
<td>• Twice daily for PI-experienced patients with certain PI mutations</td>
<td></td>
</tr>
<tr>
<td><strong>PK Boosting</strong></td>
<td>PK-boosting with RTV or COBI is generally recommended. Unboosted ATV is also FDA-approved for ART-naive patients.</td>
<td>DRV should only be used with a PK booster (i.e., RTV or COBI).</td>
</tr>
<tr>
<td><strong>Fixed-Dose Formulation</strong></td>
<td>• ATV/c</td>
<td>• DRV/c</td>
</tr>
<tr>
<td></td>
<td>• DRV/c/TAF/FTC</td>
<td></td>
</tr>
<tr>
<td><strong>Available as a Single-Drug Tablet</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>• Jaundice</td>
<td>• Skin rash</td>
</tr>
<tr>
<td></td>
<td>• Indirect hyperbilirubinemia</td>
<td>• Increase in serum transaminases</td>
</tr>
<tr>
<td></td>
<td>• Cholelithiasis</td>
<td>• Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>• Nephrolithiasis</td>
<td>• A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.</td>
</tr>
<tr>
<td><strong>CYP3A4 Drug-Drug Interactions</strong></td>
<td>CYP3A4 substrate, inhibitor</td>
<td>CYP3A4 substrate, inhibitor</td>
</tr>
<tr>
<td><strong>Other Significant Drug Interactions</strong></td>
<td>ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 19a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Key to Acronyms: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

FDA-approved PIs include ATV, ATV/c, DRV, DRV/c, fosamprenavir (FPV), indinavir (IDV), LPV/r, nelfinavir (NFV), RTV, saquinavir (SQV), and tipranavir (TPV). PI-based regimens with PK enhancement (also called boosting) have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance. Because transmitted PI resistance is uncommon, PI-based regimens are generally recommended if early ART initiation is necessary, before resistance test results are available. Few or no PI mutations are detected when a patient’s first PI-based regimen fails, which is not the case with NNRTI-based regimens and some INSTI-based regimens.134,135 For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy due to poor adherence. All PIs (boosted by either RTV or COBI) inhibit the CYP3A4 isoenzyme, which may lead to significant drug-drug interactions (see Drug-Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of recommended PIs are listed in Table 9 and Appendix B, Table 3.

PIs that are recommended for use in ART-naive patients should have proven virologic efficacy, once-daily dosing, a lower pill count than older PI-based regimens, and good tolerability. On the basis of these criteria, the Panel considers once-daily DRV/r, DRV/c, ATV/c, or ATV/r together with two NRTIs as PI-based regimen options in the category of Recommended Initial Regimens in Certain Clinical Situations. DRV/c/TAF/FTC is now available as an STR. In a large, randomized controlled trial comparing DRV/r, ATV/r,
and RAL, each administered in combination with TDF/FTC, all three regimens achieved similar virologic suppression rates; however, the proportion of patients who discontinued their assigned treatment because of adverse effects, mainly hyperbilirubinemia, was greater in the ATV/r arm than in the other two arms.11

Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.18-20,23 Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens compared to those receiving other regimens.22 Further study is needed.

Compared to other PIs, LPV/r, FPV/r, unboosted ATV, and SQV/r have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are no longer included as options for initial therapy.

**Darunavir/Ritonavir (DRV/r)**

**Efficacy in Clinical Trials:**
- The ARTEMIS study compared DRV/r (800 mg/100 mg once daily) with LPV/r (800 mg/200 mg once daily or 400 mg/100 mg twice daily), both administered in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at week 48,64 and superior at week 192.136 Among participants with baseline HIV RNA levels >100,000 copies/mL, virologic response rates were lower in the LPV/r arm than in the DRV/r arm.
- The FLAMINGO study compared DRV/r with DTG, each administered in combination with two NRTIs, in 488 ART-naive participants. The rate of virologic suppression at week 96 was significantly greater among those who received DTG than in those who received DRV/r. The excess failure observed in the DRV/r group was primarily related to a higher rate of virologic failure among those with a viral loads >100,000 copies/mL and secondarily due to more drug discontinuations in the DRV/r group.14
- ACTG A5257, a large randomized open-label trial, compared ATV/r with DRV/r or RAL, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.11
- **The DRIVE-FORWARD study compared DRV/r to DOR, both administered with two investigator-selected NRTIs, in ARI-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR achieving HIV RNA levels <50 copies/mL compared with 84% of participants who received DRV/r.**

**Adverse Effects:**
- Patients taking DRV/r may develop a skin rash, which is usually mild-to-moderate in severity and self-limited. Treatment discontinuation is necessary on rare occasions when severe rash with fever or elevated transaminases occur.
- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.11 The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P \leq 0.02$).137
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.23
Other Factors and Considerations:

- DRV/r is administered once daily with food in treatment-naive patients.
- DRV has a sulfonamide moiety and should be used with caution in patients with severe sulfonamide allergies. In clinical trials, the incidence and severity of rash were similar in participants who did or did not have a history of sulfonamide allergy. Most patients with sulfonamide allergy are able to tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, and this may lead to significant interactions with other medications metabolized through this same pathway (see Drug-Drug Interactions).

The Panel’s Recommendations:

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with TDF/FTC (AI), with TAF/FTC (AII), or with ABC/3TC (BII) as Recommended Initial Regimens in Certain Clinical Situations.

Darunavir/Cobicistat (DRV/c)

A combination of DRV 800 mg with COBI 150 mg is bioequivalent to DRV 800 mg with RTV 100 mg in healthy volunteers, based on the maximum concentration and area under the concentration time curve for DRV. Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that of DRV combined with RTV, bioequivalence for the C_{min} was not achieved.

Efficacy in Clinical Trials:

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the STR DRV/c/TAF/FTC and DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of the study (91% and 88%, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group. In the DRV plus TAF/FTC arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.

- In a single-arm trial in which most of the patients were treatment-naive (94%), the coformulated DRV/c 800 mg/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.

Adverse Effects:

- The most common drug-related adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.

Other Factors:

- DRV/c 800 mg/150 mg is available as a coformulated boosted PI or as an STR with TAF/FTC 10 mg/200 mg.

The Panel’s Recommendations:

- The Panel recommends DRV/c plus TAF/FTC or TDF/FTC (AI) and DRV/c plus ABC/3TC (BII) as Recommended Initial Regimens in Certain Clinical Situations.
- DRV/c plus TDF/FTC is not recommended for patients with CrCl <70 mL/min, whereas DRV/c plus TAF/FTC is not recommended for patients with CrCl <30 mL/min.

Atazanavir/Ritonavir (ATV/r) or Atazanavir/Cobicistat (ATV/c)

Efficacy in Clinical Trials:

- ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs
• The CASTLE study compared once-daily ATV/r (300 mg/100 mg) with twice-daily LPV/r (400 mg/100 mg), each administered in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.141

**ATV/r plus Two NRTIs versus EFV plus Two NRTIs**

• The ACTG A5202 study compared open-label ATV/r and EFV, each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.116 In a separate analysis, women assigned to receive ATV/r were found to have a higher risk of virologic failure than women assigned to receive EFV or men assigned to receive ATV/r.142

**ATV/r plus Two NRTIs versus INSTI plus Two NRTIs**

• In a study that compared ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.104 A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.15 At week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm discontinued therapy because of adverse events, compared to five women in the INSTI arm.

• In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, DTG was found to have a rate of virologic suppression (<50 copies/mL) that was noninferior to the rate seen in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.92

**ATV/r plus Two NRTIs versus DRV/r plus Two NRTIs versus RAL plus Two NRTIs**

• In ACTG A5257, a significantly higher proportion of patients in the ATV/r arm discontinued randomized treatment because of adverse events, mostly for elevated indirect bilirubin/jaundice or gastrointestinal toxicities. Lipid changes in participants in the ATV/r and DRV/r arms were similar. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.11

**ATV/c versus ATV/r plus Two NRTIs**

• In the Gilead Study 114, all patients received TDF/FTC and ATV and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.143 Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentage of adverse events that caused patients to discontinue treatment and changes in serum creatinine and indirect bilirubin levels were comparable.144

**Adverse Effects:**

• The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.145

• Nephrolithiasis,146-148 nephrotoxicity,21 and cholelithiasis149 have also been reported in patients who received ATV.

• Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

**Other Factors and Considerations:**

• ATV/c and ATV/r are dosed once daily and with food.

• ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly PPIs) may impair absorption of ATV. Table 19a provides
recommendations for use of ATV/c or ATV/r with these agents.

- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug-Drug Interactions).

- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV. Another study of an observational cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens compared with participants receiving other regimens. Further study is needed.

The Panel’s Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC (BII) or TDF/FTC (BI) as Recommended Initial Regimens in Certain Clinical Situations.

- ATV/c or ATV/r plus ABC/3TC is no longer included in the list of Recommended Initial Regimens in Certain Clinical Situations, because it has disadvantages when compared with other regimens in this category. In a randomized trial, when combined with ATV/r, ABC/3TC was less potent than TDF/FTC in people with HIV RNA >100,000 copies/mL.

- ATV/c plus TDF/FTC is not recommended for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC is not recommended for patients with CrCl <30 mL/min.

Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

All currently recommended ARV regimens consist of two NRTIs plus a third active drug. This strategy, however, may not be possible or optimal in all patients. In some situations, it may be necessary to avoid ABC, TAF, and TDF, such as in patients who are HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment. To address these concerns, several clinical studies have evaluated strategies using initial regimens that avoid the use of two NRTIs or the NRTI drug class altogether. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of patients with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

Strategies Supported by Evidence from Clinical Trials

Dolutegravir plus Lamivudine (DTG plus 3TC)

- In the GEMINI-1 and -2 trials, a total of 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At week 48, DTG plus 3TC was noninferior to DTG plus TDF/FTC with respect to the proportion of participants with viral loads <50 copies/mL (91% and 93%, respectively). Virologic nonresponse was uncommon, occurring in 3% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or INSTI resistance occurred in either treatment group. Longer term follow up is ongoing.

- The PADDLE trial was a small, single-arm study of DTG plus 3TC in 20 ART-naive adults with baseline HIV RNA <100,000 copies/mL. At 48 weeks, 18 out of 20 subjects (90%) achieved HIV RNA <50 copies/mL. Fifteen of these 18 participants completed 96 weeks of treatment and maintained HIV RNA <50 copies/mL.

- The ACTG A5353 trial evaluated this same regimen in a single-arm trial that included ART-naive participants with a baseline HIV RNA of up to 500,000 copies/mL and no genotypic NRTI, INSTI, or PI resistance. The trial enrolled 120 participants; 37 participants (30.8%) had a baseline HIV RNA >100,000 copies/mL.
copies/mL. At week 24, 90% of participants had HIV RNA <50 copies/mL; there were similar response rates in participants with baseline HIV RNA >100,000 copies/mL and ≤100,000 copies/mL (89% and 90%, respectively). Three participants experienced virologic failure, all of whom had suboptimal adherence; one participant developed an NRTI resistance mutation (M184V) and an INSTI resistance mutation (R263K).132

The Panel’s Recommendation:

• On the basis of these study results, the Panel recommends the use of DTG plus 3TC in ART-naive adults with baseline HIV RNA <500,000 copies/mL in instances where ABC, TAF, or TDF cannot be used or are not optimal (BI).

• Preliminary data from an observational study in Botswana suggest that there may be an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.6,7 Clinicians should refer to Table 6b prior to initiation of DTG in those who are pregnant or those who are of childbearing potential.

Darunavir/Ritonavir plus Lamivudine (DRV/r plus 3TC)

• In the ANDES trial, 145 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 log10 copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.25 The dual- and triple-therapy groups had similar rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL (91% and 92%, respectively).

The Panel’s Recommendation:

• On the basis of results from a small study with a relatively short follow-up period, DRV/r plus 3TC can be considered for use in people who cannot take ABC, TAF, or TDF (CI). Although the ANDES trial supports the use of DRV/r plus 3TC, it is smaller than other trials of NRTI-limiting regimens, and larger studies are warranted.

Darunavir/Ritonavir plus Raltegravir (DRV/r plus RAL)

• In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 cell counts <200 cells/mm³, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.24 High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.153,154

The Panel’s Recommendation:

• On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 cell counts >200 cells/mm³, and only in those patients who cannot take ABC, TAF, or TDF (CI).

A Nucleoside-Limiting Regimen that is Efficacious but has Disadvantages

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

• In the GARDEL study, 426 ART-naive patients were randomized to receive twice-daily LPV/r plus either
open-label 3TC (twice daily) or two NRTIs selected by the study investigators. At 48 weeks, a similar proportion of patients in each arm had HIV RNA <50 copies/mL (88.3% vs. 83.7%), meeting the study’s noninferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus two NRTI regimen.155

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

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 5)

Note: All drugs within an ARV class are listed in alphabetical order.

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual-NRTI</td>
<td>ABC/3TC</td>
<td>• Coformulated with DTG&lt;br&gt;• Generic formulations are available for ABC/3TC, ABC, and 3TC.</td>
<td>• May cause life-threatening HSRs in patients who test positive for the HLA-B<em>5701 allele. As a result, HLA-B</em>5701 testing is required before use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection&lt;br&gt;• Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC&lt;br&gt;• Approved for patients with eGFR ≥30 mL/min</td>
<td>• ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.</td>
</tr>
<tr>
<td></td>
<td>TAF/FTC</td>
<td>• Coformulated with BIC, DRV/r, EVG/c, or RPV&lt;br&gt;• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection&lt;br&gt;• Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC&lt;br&gt;• Approved for patients with eGFR ≥30 mL/min</td>
<td>• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids.</td>
</tr>
<tr>
<td></td>
<td>TDF/3TC</td>
<td>• Coformulated with DOR and EFV&lt;br&gt;• Available as the following generic formulations: TDF&lt;br&gt;• 3TC&lt;br&gt;• TDF/3TC&lt;br&gt;• EFV/TDF/3TC&lt;br&gt;• Long-term clinical experience&lt;br&gt;• Active against HBV</td>
<td>• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters.&lt;br&gt;• Osteomalacia has been reported as a consequence of proximal tubulopathy.&lt;br&gt;• Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
<td>• Coformulated with EFV, EVG/c, and RPV as STRs&lt;br&gt;• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection&lt;br&gt;• Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV&lt;br&gt;• Associated with lower lipid levels than ABC or TAF</td>
<td>• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters.&lt;br&gt;• Osteomalacia has been reported as a consequence of proximal tubulopathy.&lt;br&gt;• Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.</td>
</tr>
</tbody>
</table>
### Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 5)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
</table>
| INSTI     | BIC          | • Coformulated with TAF/FTC  
• In trials in ART-naive participants, BIC resistance was not detected  
• No food requirement | • Compared to other INSTIs, BIC has the shortest post-marketing experience.  
• Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.  
• Inhibits tubular secretion of creatinine without affecting glomerular function.  
• CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug interactions. |
|           |              | • Higher barrier to resistance than EVG or RAL  
• Coformulated with ABC and 3TC  
• No food requirement  
• No CYP3A4 interactions  
• Favorable lipid profile | • Preliminary data suggests that DTG use before pregnancy and through conception may be associated with an increased risk of NTDs in the infant. See text and Table 6b for recommendations.  
• Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.  
• Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function.  
• UGT1A1 substrate; potential for drug interactions (see Table 19d).  
• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). |
|           | EVG/c        | • Coformulated with TDF/FTC or TAF/FTC  
• Compared with ATV/r, causes smaller increases in total and LDL cholesterol | • EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min.  
• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.  
• Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.  
• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function.  
• Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens.  
• Food requirement.  
• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). |
### Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 5)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
</table>
| INSTI, continued | RAL | • Compared to other INSTIs, has longest post-marketing experience  
• No food requirement  
• No CYP3A4 interactions  
• Favorable lipid profile | • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens.  
• Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported.  
• Rare cases of severe HSRs (including SJS and TEN) have been reported.  
• Higher pill burden than other INSTI-based regimens.  
• No STR formulation.  
• Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.  
• UGT1A1 substrate; potential for drug interactions (see Table 19d).  
• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). | |
| NNRTI    | DOR | • Coformulated with TDF/3TC  
• Compared to EFV, CNS side effects are less frequent  
• No food requirement  
• Favorable lipid profile | • Shorter-term clinical experience than with EFV and RPV.  
• Potential for CYP450 drug interactions (see Tables 19b, 20a and 20b).  
• Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs. | |
| EFV      |   | • EFV 600 mg is coformulated with TDF/FTC and TDF/3TC  
• EFV 600 mg is coformulated with TDF/3TC  
• EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA | • Short-and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV.  
• Teratogenic in nonhuman primates, although no rate increase has been seen in humans.  
• Dyslipidemia  
• Rash  
• QTc interval prolongation; consider using an alternative to EFV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.  
• Transmitted resistance is more common than with PIs and INSTIs.  
• Greater risk of resistance at the time of treatment failure than with PIs.  
• Potential for CYP450 drug interactions (see Tables 19b and 20a).  
• Should be taken on an empty stomach (food increases drug absorption and CNS toxicities). | |
### Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 5)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
</table>
| NNRTI, continued | RPV | • Coformulated with TDF/FTC and TAF/FTC  
• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs  
• Compared with EFV:  
  • Fewer CNS adverse effects  
  • Fewer lipid effects  
  • Fewer rashes | • Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 cell counts <200 cells/mm³ because of higher rate of virologic failure in these patients.  
• Depression and suicidality  
• QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.  
• Rash  
• Transmitted resistance is more common than with PIs and INSTIs.  
• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.  
• Potential for CYP450 drug interactions (see Tables 19b and 20a).  
• Meal requirement (>390 kcal)  
• Requires acid for adequate absorption.  
• Contraindicated with PPIs.  
• Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information). |
| PIs | ATV/c or ATV/r | • Higher barrier to resistance than NNRTIs, EVG, and RAL  
• PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs  
• ATV/c and ATV/r have similar virologic activity and toxicity profiles  
• Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion.  
• Individual ATV and RTV components available as generics | • Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice.  
• Food requirement  
• Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs).  
• Nephrolithiasis, cholelithiasis, nephrotoxicity  
• GI adverse effects  
• CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 19a). |
| ATV/c (Specific considerations) | • Coformulated tablet | • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function.  
• Coadministration with TDF is not recommended in patients with CrCl <70 mL/min.  
• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. |
| DRV/c or DRV/r | • Higher barrier to resistance than NNRTIs, EVG, and RAL  
• PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs | • Skin rash  
• Food requirement  
• GI adverse effects  
• CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 19a).  
• Increased CV risk reported in one observational cohort study. |
### Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 5 of 5)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs, continued</td>
<td>DRV/c (Specific considerations)</td>
<td>• Coformulated as DRV/c and DRV/c/TAF/FTC</td>
<td>• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF is not recommended in patients with CrCl &lt;70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</td>
</tr>
<tr>
<td>LPV/r</td>
<td>• Only RTV-coformulated PI</td>
<td></td>
<td>• Requires RTV 200 mg per day. • Possible higher risk of MI associated with cumulative use of LPV/r. • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or in patients receiving other drugs with similar effects. • Possible nephrotoxicity • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 19a).</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed=dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV = lopinavir; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase

### Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 3)

<table>
<thead>
<tr>
<th>ARV Components or Regimens</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/ZDV (Coformulated)</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>As triple-NRTI combination regimen</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/ZDV plus TDF</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>As quadruple-NRTI combination regimen</td>
<td></td>
</tr>
<tr>
<td>d4T plus 3TC</td>
<td>• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)</td>
</tr>
<tr>
<td>ddl plus 3TC (or FTC)</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Limited clinical trial experience in ART-naive patients</td>
</tr>
<tr>
<td></td>
<td>• ddl toxicities, such as pancreatitis and peripheral neuropathy</td>
</tr>
<tr>
<td>ddl plus TDF</td>
<td>• High rate of early virologic failure</td>
</tr>
<tr>
<td></td>
<td>• Rapid selection of resistance mutations</td>
</tr>
<tr>
<td></td>
<td>• Potential for immunologic nonresponse/CD4 cell decline</td>
</tr>
<tr>
<td></td>
<td>• Increased ddl drug exposure and toxicities</td>
</tr>
</tbody>
</table>

*Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*
Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy

<table>
<thead>
<tr>
<th>ARV Components or Regimens</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs, continued</strong></td>
<td></td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>DLV</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Inconvenient (three times daily) dosing</td>
</tr>
<tr>
<td>ETR</td>
<td>• Insufficient data in ART-naive patients</td>
</tr>
<tr>
<td>NVP</td>
<td>• Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including SJS and TEN)</td>
</tr>
<tr>
<td></td>
<td>• When compared to EFV, NVP did not meet noninferiority criteria</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
</tr>
<tr>
<td>ATV (Unboosted)</td>
<td>• Less potent than boosted ATV</td>
</tr>
<tr>
<td>DRV (Unboosted)</td>
<td>• Use without RTV or COBI has not been studied</td>
</tr>
<tr>
<td>FPV (Unboosted) or FPV/r</td>
<td>• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV</td>
</tr>
<tr>
<td></td>
<td>• Less clinical trial data for FPV/r than for other RTV-boosted PIs</td>
</tr>
<tr>
<td>IDV (Unboosted)</td>
<td>• Inconvenient dosing (3 times daily with meal restrictions)</td>
</tr>
<tr>
<td></td>
<td>• Fluid requirement</td>
</tr>
<tr>
<td></td>
<td>• IDV toxicities, such as nephrolithiasis and crystalluria</td>
</tr>
<tr>
<td>IDV/r</td>
<td>• Fluid requirement</td>
</tr>
<tr>
<td></td>
<td>• IDV toxicities, such as nephrolithiasis and crystalluria</td>
</tr>
<tr>
<td>LPV/r</td>
<td>• Higher pill burden than other PI-based regimens</td>
</tr>
<tr>
<td></td>
<td>• Higher RTV dose than other PI-based regimens</td>
</tr>
<tr>
<td></td>
<td>• GI intolerance</td>
</tr>
<tr>
<td>NFV</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td>RTV as sole PI</td>
<td>• High pill burden</td>
</tr>
<tr>
<td></td>
<td>• GI intolerance</td>
</tr>
<tr>
<td></td>
<td>• Metabolic toxicity</td>
</tr>
<tr>
<td>SQV (Unboosted)</td>
<td>• Inadequate bioavailability</td>
</tr>
<tr>
<td></td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>SQV/r</td>
<td>• High pill burden</td>
</tr>
<tr>
<td></td>
<td>• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG</td>
</tr>
<tr>
<td>TPV/r</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Higher rate of adverse events than other RTV-boosted PIs</td>
</tr>
<tr>
<td></td>
<td>• Higher dose of RTV required for boosting than other RTV-boosted PIs</td>
</tr>
<tr>
<td><strong>Entry Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>T-20</td>
<td>• Only studied in patients with virologic failure</td>
</tr>
<tr>
<td>Fusion Inhibitor</td>
<td>• Twice-daily subcutaneous injections</td>
</tr>
<tr>
<td></td>
<td>• High rate of injection site reactions</td>
</tr>
<tr>
<td>IBA</td>
<td>• Only studied in a very small number of patients with virologic failure</td>
</tr>
<tr>
<td>CD4 Post-Attachment Inhibitor</td>
<td>• Requires IV therapy</td>
</tr>
<tr>
<td></td>
<td>• High cost</td>
</tr>
</tbody>
</table>
### ARV Components or Regimens

<table>
<thead>
<tr>
<th>MVC</th>
<th>CCR5 Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Requires testing for CCR5 tropism before initiation of therapy</td>
<td></td>
</tr>
<tr>
<td>• No virologic benefit when compared with other recommended regimens</td>
<td></td>
</tr>
<tr>
<td>• Requires twice-daily dosing</td>
<td></td>
</tr>
</tbody>
</table>

**Key to Acronyms:**
- 3TC = lamivudine
- ABC = abacavir
- ART = antiretroviral therapy
- ARV = antiretroviral
- ATV = atazanavir
- CD4 = CD4 T lymphocyte
- COBI = cobicistat
- d4T = stavudine
- ddI = didanosine
- DLV = delavirdine
- DRV = darunavir
- ECG = electrocardiogram
- Efavirenz
- ETR = etravirine
- FPV = fosamprenavir
- FPV/r = fosamprenavir/ritonavir
- FTC = emtricitabine
- GI = gastrointestinal
- IBA = ibalizumab
- IDV = indinavir
- IDV/r = indinavir/ritonavir
- IV = intravenous
- LPV = lopinavir
- LPV/r = lopinavir/ritonavir
- MVC = maraviroc
- NFV = nelfinavir
- NNRTI = non-nucleoside reverse transcriptase inhibitor
- NRTI = nucleoside reverse transcriptase inhibitor
- NVP = nevirapine
- PI = protease inhibitor
- RTV = ritonavir
- SJS = Stevens Johnson Syndrome
- SQV = saquinavir
- SQV/r = saquinavir/ritonavir
- T-20 = enfuvirtide
- TDF = tenofovir disoproxil fumarate
- TEN = toxic epidermal necrolysis
- TPV = tipranavir
- TPV/r = tipranavir/ritonavir
- ZDV = zidovudine

**References**

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

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019


65. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV* F-47

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019


What Not to Use (Last updated October 17, 2017; last reviewed October 17, 2017)

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

Antiretroviral Drugs Not Recommended

The following ARV drugs are no longer recommended for use because of suboptimal antiviral potency, unacceptable toxicities, high pill burden, or pharmacologic concerns: delavirdine (DLV), didanosine (ddI), indinavir (IDV), nelfinavir (NFV), and stavudine (d4T).

Antiretroviral Regimens Not Recommended

Monotherapy

Nucleoside reverse transcriptase inhibitor (NRTI) monotherapy is inferior to dual-NRTI therapy.1 Protease inhibitor (PI) monotherapy is inferior to combination antiretroviral therapy (ART).2-6 Integrase strand transfer inhibitor (INSTI) monotherapy has resulted in virologic rebound and INSTI resistance (AI).7,8

Dual-NRTI Regimens

These regimens are inferior to triple-drug combination regimens (AI).9

Triple-NRTI Regimens

Triple-NRTI regimens have suboptimal virologic activity10-12 or a lack of data (AI).

Antiretroviral Components Not Recommended

Atazanavir plus Indinavir

Both PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly (AIII).

Cobicistat plus Ritonavir as Pharmacokinetic Enhancers

This combination may be prescribed inadvertently, which may result in additive CYP3A4 enzyme inhibition and may further increase the concentrations of ARV drugs or other concomitant medications (see Tables 19a and 19d).

Didanosine plus Stavudine

The combination of ddI and d4T can result in peripheral neuropathy, pancreatitis, and lactic acidosis, and it has been implicated in the deaths of several pregnant women (AII).13

Didanosine plus Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) increases ddI concentrations,14 serious ddI-associated toxicities,15,16 immunologic nonresponse,17 early virologic failure,18,19 and resistance18,20 (AII).

Two Non-Nucleoside Reverse Transcriptase Inhibitor Combinations

Excess clinical adverse events and treatment discontinuation were reported in patients randomized to receive treatment with two non-nucleoside reverse transcriptase inhibitors (NNRTIs).21 Efavirenz (EFV) and nevirapine (NVP) are enzyme inducers, and both of these drugs can reduce concentrations of etravirine (ETR) and rilpivirine (RPV) (AI).22
Emtricitabine plus Lamivudine
Both drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur in vivo (AIII).23

Etravirine plus Unboosted Protease Inhibitor
ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established (AII).22

Etravirine plus Fosamprenavir/Ritonavir
ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established (AII).22

Etravirine plus Tipranavir/Ritonavir
Tipranavir/ritonavir (TPV/r) significantly reduces ETR concentrations (AII).22

Nevirapine Initiated in ARV-Naive Women with CD4 Counts >250 cells/mm³ or in ARV-Naive Men with CD4 Counts >400 cells/mm³
Initiating NVP below these CD4 count thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.24-26 Patients with CD4 counts above these thresholds due to ART can safely switch to NVP (BI).27

Unboosted Darunavir, Saquinavir, or Tipranavir
The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV, or in the case of DRV, also with COBI (AII).

Stavudine plus Zidovudine
These NRTIs are antagonistic in vitro28 and in vivo29 (AII).

Tenofovir Alafenamide plus Tenofovir Disoproxil Fumarate
This combination may be prescribed inadvertently, especially during transition from one formulation to another. There is no data supporting any potential additive efficacy or toxicity if TAF and TDF are used in combination.

References


### 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 rebound⁹,¹⁰ 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.\textsuperscript{14,15} The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.\textsuperscript{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).\(^31\) 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 strand 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). 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. 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. 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. 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. Lower rates of virologic suppression were seen with LPV/r monotherapy, confirming that ritonavir-boosted PI (PI/r) monotherapy cannot be recommended (AI). 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. 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. 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. 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. 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. 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). 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. Viruses with EVG or RAL resistance often remain susceptible to DTG. 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. 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 log₁₀ 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 AIDSinfo’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.

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. 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.

### 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.

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Type of Failing Regimen</th>
<th>Resistance Considerations</th>
<th>New Regimen Optionsa,b</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Regimen Failure</strong></td>
<td>NNRTI plus 2 NRTIs</td>
<td>Most likely resistant to NNRTI +/- 3TC/FTC (i.e., NNRTI mutations +/- M184V/I). Additional NRTI mutations may also be present.</td>
<td>• Boosted PI plus 2 NRTIs (at least 1 active) (AIII); or&lt;br&gt;• DTGd plus 2 NRTIs (at least 1 active) (AI); or&lt;br&gt;• Boosted PI plus INSTI (AIII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td>Boosted PI plus 2 NRTIs</td>
<td>Most likely no resistance, or resistance only to 3TC/FTC (i.e., M184V/I, without resistance to other NRTIs)</td>
<td>• Continue same regimen (AII); or&lt;br&gt;• Another boosted PI plus 2 NRTIs (at least 1 active) (AII); or&lt;br&gt;• INSTI plus 2 NRTIs (at least 1 active; if only 1 of the NRTIs is fully active, or, if adherence is a concern, DTGd is preferred over the other INSTIs) (AIII); or&lt;br&gt;• Another boosted PI plus INSTI (BIII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td></td>
<td>INSTI plus 2 NRTIs</td>
<td>No INSTI resistance (can have 3TC/FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs)</td>
<td>• Boosted PI plus 2 NRTIs (at least 1 active) (AII); or&lt;br&gt;• DTGd plus 2 NRTIs (at least 1 active) (AIII); or&lt;br&gt;• Boosted PI plus INSTI (BIII)</td>
<td>Resuppression</td>
</tr>
<tr>
<td>Clinical Scenario</td>
<td>Type of Failing Regimen</td>
<td>Resistance Considerations</td>
<td>New Regimen Options(^{a,b})</td>
<td>Goal</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>First Regimen Failure, continued</td>
<td>INSTI plus 2 NRTIs</td>
<td>EVG or RAL +/- 3TC/FTC resistance</td>
<td>• Boosted PI plus 2 NRTIs (at least 1 active) (AI); or&lt;br&gt;• DTG(^{d,e}) twice daily (if patient is sensitive to DTG) plus 2 active NRTIs (AI); or&lt;br&gt;• DTG(^{d,e}) twice daily (if patient is sensitive to DTG) plus a boosted PI (AI)&lt;br&gt;<strong>BIC has not been studied in this setting and cannot be recommended.</strong></td>
<td>Resuppression</td>
</tr>
<tr>
<td>Second Regimen Failure and Beyond</td>
<td>Drug resistance with active treatment options</td>
<td>Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen</td>
<td>• At least 2, and preferably 3, fully active agents (AI)&lt;br&gt;• Partially active drugs may be used when no other options are available&lt;br&gt;• Consider using an ARV with a different mechanism of action</td>
<td>Resuppression</td>
</tr>
<tr>
<td>Previously on Treatment, Suspected Drug Resistance, Limited or Incomplete ART and Resistance History</td>
<td>Unknown</td>
<td>Obtain medical records if possible&lt;br&gt;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.</td>
<td>• Consider restarting the old regimen, and obtain viral load and resistance testing 2–4 weeks after reintroduction of therapy&lt;br&gt;• 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)&lt;br&gt;<strong>Discontinuation of ARVs is not recommended.</strong></td>
<td>Resuppression</td>
</tr>
</tbody>
</table>

\(^{a}\) 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. Clinical evaluation frequently shows abnormalities on magnetic resonance imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis. 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).

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, 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).

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. Unlike the “neurosymptomatic” CNS viral escape, these latter conditions do not currently warrant a change in ART.

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.

References


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


Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV
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 (AI).
- 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) (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

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. 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/mm³); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm³) 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 cell counts <200 cells/mm³ 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, liver disease, and infection-related cancers. 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/mm³.

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, or the combination of tenofovir disoproxil fumarate [TDF] and didanosine [ddl]). 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/mm³. 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, 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). 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).

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. 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. 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. Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm³) tend to have greater immune activation and inflammation than those with greater recovery, the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count. Even in individuals with CD4 counts >500 cells/mm³, there is evidence that immune activation and inflammation contribute to morbidity and mortality. 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. 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.
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, 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. 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).

References


Panel's Recommendations

- 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. 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. 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.34

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\textsuperscript{5,6} or abacavir (ABC)\textsuperscript{7} to TAF
- RAL to elvitegravir/cobicistat (EVG/c)\textsuperscript{8} or DTG
- DTG\textsuperscript{8,10}, EVG/c, or RAL to BIC
- Efavirenz (EFV) to RPV\textsuperscript{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)\textsuperscript{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\textsuperscript{15}, BIC\textsuperscript{16}, or EVG\textsuperscript{17,18})
- Replacing a boosted PI with RPV\textsuperscript{19}
- Replacing an NNRTI with an INSTI\textsuperscript{20,21}
- Replacing a boosted PI with maraviroc (MVC)\textsuperscript{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\textsuperscript{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.\textsuperscript{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),\textsuperscript{26,27}
- Darunavir/ritonavir (DRV/r) plus 3TC (BI),\textsuperscript{28} or
- Lopinavir/ritonavir (LPV/r) plus 3TC (CI).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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%.\textsuperscript{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. 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. 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, as well as in a randomized controlled trial. 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. 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).

**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. 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).
References


Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel’s Recommendations

- Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of patients with HIV (BII).
- TDM may be considered in selected clinical scenarios, as discussed in the text below.

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

Knowledge about the relationship between a drug’s systemic exposure (or concentration) and responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding why patients may respond differently to the same drug and dose, and in designing strategies to optimize drug response and tolerability.

Therapeutic drug monitoring (TDM) is a strategy used to guide dosing of certain antiarrhythmics, anticonvulsants, antineoplastics, and antimicrobial agents by using measured drug concentrations to improve the likelihood of the desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Several antiretroviral (ARV) agents meet most of the characteristics of agents suitable for a TDM strategy. Specifically, some ARVs have considerable interpatient variability in drug concentrations. Other ARVs have known drug concentrations associated with efficacy and/or toxicity. In the case of other drugs, data from small prospective studies have demonstrated that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.

TDM for ARV agents, however, is not recommended for routine use in the management of adults and adolescents with HIV (BII). This recommendation is based on multiple factors that limit the routine use of TDM in patients with HIV. These limiting factors include lack of prospective studies that demonstrate routine use of TDM improves clinical outcomes, uncertain therapeutic thresholds for most ARV agents, great intra- and inter-patient variability in drug concentrations achieved, and a lack of commercial laboratories to perform real time quantitation of ARV concentrations.

Scenarios for Consideration of Therapeutic Drug Monitoring

Although routine use of TDM is not recommended, in some scenarios, ARV concentration data may be useful in patient management. In these cases, assistance from a clinical pharmacologist or a clinical pharmacist to interpret the concentration data may be advisable. These scenarios include the following:

- Suspicion of clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Among pregnant women who have risk factors for virologic failure (e.g., those not achieving viral suppression during an earlier stage of pregnancy), physiologic changes may result in reduced drug exposure during the later stages of pregnancy and thus further increase the risk of virologic failure;
- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
• Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;

• Concentration-dependent, drug-associated toxicities; and

• Failure to achieve expected virologic response in medication-adherent patients.

**Resources for Therapeutic Drug Monitoring Target Concentrations**

Most TDM-proposed target concentrations for ARVs focus on a minimum concentration (C_{min}) (i.e., the plasma concentration at the end of a dosing interval before the next ARV dose). A summary of population average ARV C_{min} can be found in a review on the role of ARV-related TDM. Population average C_{min} for newer ARVs can be found in the Food and Drug Administration-approved product labels.

Guidelines for the collection of blood samples and other practical suggestions related to TDM can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.

**Challenges and Considerations in Using Drug Concentrations to Guide Therapy**

There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires the following:

• Quantification of the concentration of the drug, usually in plasma or serum;

• Determination of the patient’s pharmacokinetic characteristics;

• Integration of information on patient adherence;

• Interpretation of the drug concentrations; and

• Adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information, including the patient’s ARV history and adherence before the TDM result. In addition, as knowledge of associations between ARV concentrations and virologic response evolves, clinicians who use a TDM strategy for patient management should evaluate the most up-to-date information regarding the exposure-response relationship of the tested ARV agent.

**References**


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.

References


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 earlya HIV-1 infection.
- Once initiated, the goal of ART is to suppress plasma HIV-1 RNA to undetectable levels (AII). 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 (AII). 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 (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 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, a recent prospective study shows that most patients have nonspecific and relatively mild signs and symptoms. 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). 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. 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. 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.

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). 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. 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. In addition, because early HIV-1 infection is often associated with high viral loads and increased infectiousness, and the use of antiretroviral therapy (ART) by individuals with HIV reduces the risk of transmission to sexual partners without HIV, 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.
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. In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least one drug. 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. 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

<table>
<thead>
<tr>
<th>Suspicion of Acute HIV-1 Infection:</th>
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<tbody>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
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<th>Differential Diagnosis:</th>
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<tr>
<td>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.</td>
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<tr>
<th>Evaluation/Diagnosis of Acute HIV-1 Infection:</th>
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<tr>
<td>• 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.</td>
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<tr>
<td>• A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
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<tr>
<th>Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:</th>
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<tbody>
<tr>
<td>• ART is recommended for all individuals with HIV-1 (AI) and should be offered to all patients with early HIV-1 infection.</td>
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<tr>
<td>• A pregnancy test should be performed for all individuals who receive a diagnosis of early HIV infection and who are of childbearing potential (AIII).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• 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:</td>
</tr>
<tr>
<td>• Who are pregnant and within 12 weeks post-conception (AII);</td>
</tr>
<tr>
<td>• Who are of childbearing potential, who are sexually active, and who are not using effective contraception (AII); or</td>
</tr>
<tr>
<td>• Who are contemplating pregnancy (AII).</td>
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<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• Once initiated, the goal of ART should be sustained plasma virologic suppression, and ART should be continued indefinitely (AIII).</td>
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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

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV
Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019
References


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).

Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV. 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. 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. 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. 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. In an ARV treatment trial, a cohort of ART-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance. 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. 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, more intensive case management approaches may be considered for adolescents with HIV. Adolescents may seek care in several settings, including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics. When available, youth services may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents. Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.

**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. 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. 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. Directly observed therapy may be considered for some adolescents with HIV, such as those with mental illness.

**Difficult Adherence Problems**

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and lifestyle, 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 the Adherence to the Continuum of Care in these guidelines and the Pediatric Guidelines.

**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. For a more detailed discussion on STIs, see the most recent CDC guidelines, Adult and Adolescent Opportunistic Infections Guidelines, and Pediatric Opportunistic Infections Guidelines on HPV among adolescents with HIV. 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.36 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.

References


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


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.

**References**


Women with HIV  

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 (BII).
- 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). 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{11,12} Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, male circumcision, and/or self-insemination with the sperm of the partner without HIV during the periovulatory period of the individual with HIV.

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. Several regimens that include a cobicistat-boosted PI, PI/r, and EVG/c decrease oral contraceptive estradiol levels. One PK study showed that DTG did not affect ethinyl estradiol or norgestimate levels. 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.

• 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, nefilnavir (NFV), or NRTI drugs. 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.

• Contraceptive Implants: Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported. Studies of women with levonorgestrel- and etonogestrel-releasing implants reported that participants receiving EFV-based ART had decreased bioavailability of levonorgestrel and...
etongestrel.\textsuperscript{45-47} These studies did not identify any change in hormone concentrations when the implants were used in those taking NVP\textsuperscript{45,47} or LPV/r.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).
References


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

<table>
<thead>
<tr>
<th>Summary of HIV-2 Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• A few laboratories now offer quantitative plasma HIV-2 RNA testing for clinical care (see section text).</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management.</td>
</tr>
</tbody>
</table>

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 immunologic 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

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

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019
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; 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) and to enfuvirtide (T-20). 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. Darunavir (DRV), lopinavir (LPV), and saquinavir (SQV) are more active against HIV-2 than other approved protease inhibitors (PIs); 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*. The CCR5 antagonist maraviroc (MVC) appears active against some HIV-2 isolates; 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.

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. Clinical data on the effectiveness of triple-NRTI regimens are conflicting. 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. However, CD4 cell recovery on therapy is generally poorer than that observed for HIV-1. INSTI-based regimens may also have favorable treatment responses. 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.

Resistance-associated viral mutations to NRTIs, PIs, and/or INSTIs commonly develop in patients with HIV-2 while on therapy. Currently, HIV-2 transmitted drug resistance appears rare. 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. 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.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection; 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.

References


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. 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. 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. 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. 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. 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, and tended to present to care with significantly lower CD4 counts. 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. Despite CDC guidelines recommending HIV testing at least...
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, 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. However, other studies show the immunologic changes to be distinct from age-related changes. In addition, although data on the increased incidence and prevalence of age-associated comorbidities in patients with HIV are accumulating, the age of diagnosis for myocardial infection and non-AIDS cancers in patients who have HIV and those who do not is the same.

- 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, 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). 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. However, ART-associated CD4 cell recovery in older patients is generally slower and lower in magnitude than in younger patients. 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. 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. 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. 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. 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. 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. Neurocognitive impairment, already a major health problem in aging adults, may be exacerbated by the effect of HIV infection on the brain. In a prospective observational study, neurocognitive impairment was predictive of lower retention in care among older persons. 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. Heart disease and cancer are the leading causes of death in older Americans. 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.
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.

**References**


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 (AII).

• If TDF or TAF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BII). 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 HIV/HBV-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; \(P = .47\)). 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; \(P = .25\)). 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. 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). 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. 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). 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. 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. 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).

References


13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for


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 mono-infection.8 The risk of progression is even greater in patients with HCV/HIV coinfection who have low CD4 T lymphocyte cell counts.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 diagnosis. Screening for HCV infection should be considered annually in patients at increased risk, such as those with a history of intravenous drug use, injection drug use, or receipt of blood products before 1992.4,15

**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 (HBeAb; 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 panel recommends that all people with HIV be screened for HCV infection using sensitive immunoassays licensed for diagnosis. Screening for HCV infection should be considered annually in patients at increased risk, such as those with a history of intravenous drug use, injection drug use, or receipt of blood products before 1992.4,15
the detection of antibodies to HCV in blood. 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 DAAAs. 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.\textsuperscript{18} Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.\textsuperscript{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](https://aidsinfo.nih.gov/guidelines). 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.

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<tr>
<th>Selected HIV Drugs</th>
<th>HCV Direct-Acting Antiviral Agents</th>
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Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

J-9

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019
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)

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<th>Selected HIV Drugs</th>
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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)

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<th>Selected HIV Drugs</th>
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<td>Glecaprevir/Pibrentasvir</td>
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<td>Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvira</td>
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<tr>
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Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

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### 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
References


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

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### 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. 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.

### 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. 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 coadministered 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. 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. 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)\(^7\) \textbf{(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 \textbf{Tables 19a through 19e}).

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.

\textbf{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.

\textbf{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 (\textbf{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 \textbf{(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.

\textbf{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 \textbf{Tables 19a through 19e} for dosing recommendations).

\textbf{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. 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. 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 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. Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients, 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; \( P = 0.04 \)). 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).

**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.\textsuperscript{20} Tables 19a through 19e 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.\textsuperscript{21,22} Several observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of EFV.\textsuperscript{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,\textsuperscript{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 19e for dosing recommendations).

Rifapentine is a long-acting rifamycin which can be given once weekly with INH to treat latent TB infection.\textsuperscript{26} Once-daily rifapentine is a more potent inducer than daily rifampin therapy.\textsuperscript{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\textsuperscript{28} and has minimal impact on EFV exposure when given once weekly,\textsuperscript{6} whereas once-weekly rifapentine led to increase instead of decrease in RAL drug exposure in healthy volunteers.\textsuperscript{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.\textsuperscript{29,30} Predictors of IRIS include a baseline CD4 count <50 cells/mm\textsuperscript{3}; higher on-ART CD4 counts; higher 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.\textsuperscript{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. 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).

References

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

J-18

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Limitations to Treatment Safety and Efficacy

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

<table>
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<th>Key Summary of Adherence to the Continuum of Care</th>
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<td>• Linkage-to-care and adherence to both antiretroviral therapy (ART) and clinic appointments should be regularly assessed.</td>
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<td>• An individual’s barriers to adherence to ART and appointments should be assessed before initiation of ART and regularly thereafter.</td>
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<tr>
<td>• 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.</td>
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<td>• Patients having difficulties with adherence to appointments or ART should be approached in a constructive, collaborative, nonjudgmental, and problem-solving manner.</td>
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<td>• 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:</td>
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<td>• Changing ART to simplify dosing or reduce side effects</td>
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<td>• Finding resources to assist with treatment costs to maintain uninterrupted access to both ART and appointments</td>
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<td>• Allowing flexible appointment scheduling</td>
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<td>• Assisting with transportation, or</td>
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<td>• Linking patients to counseling to overcome stigma, substance use, or depression.</td>
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<tr>
<td>• 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.</td>
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<td>• A summary of best practice interventions to improve linkage, retention, and adherence can be found at a Centers for Disease Control and Prevention compendium (<a href="https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html">https://www.cdc.gov/hiv/research/interventionresearch/compendium/index.html</a>).</td>
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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. 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. 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%. Outcomes along the continuum also vary by geographic region and other population characteristics, such as sex, race/ethnicity, and HIV risk factors. 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. 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 services11 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, peer support, and engaging with the patient at the clinic in advance of the visit with the provider. Financial incentives did not increase linkage to care within 90 days in a large randomized trial.

**Retention in Care**

Poor retention in HIV care is associated with greater risk of death. 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. 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. 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. 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. Both approaches are valid and independently predict survival. 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. In-clinic opioid replacement therapy helps opioid users remain in care. 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. 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. 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,
- Stepped case management and social and outreach services,
- “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). 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. 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. 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%. 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. 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. 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).

Characteristics of one or more components of the prescribed regimen can affect adherence. Once-daily regimens, 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. 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. 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. 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. 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](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](https://aidsinfo.nih.gov/guidelines/K-5/0). 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.\textsuperscript{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.\textsuperscript{71} Problem-solving approaches that vary in intensity and culturally tailored approaches also are promising.\textsuperscript{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\textsuperscript{74} but not to patients in a general clinic population\textsuperscript{75} or in home-based settings with partners responsible for DOT.\textsuperscript{76} The use of incentives or rewards to promote adherence has been studied, and they have been shown to improve adherence in one study.\textsuperscript{19} However, the durability and feasibility of financial incentives are not known at this time, hence rewards for adherence are not generally recommended.\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide an accessible, trustworthy, nonjudgmental multidisciplinary health care team.</td>
<td>• Care providers, nurses, social workers, case managers, pharmacists, and medication managers.</td>
</tr>
</tbody>
</table>
| 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 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)

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Examples</th>
</tr>
</thead>
</table>
| 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](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

**References**


73. de Bruin M, Oberje EJM, Viechtbauer W, et al. Effectiveness and cost-effectiveness of a nurse-delivered intervention to...


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 steatosis2,3 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.
Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 1 of 5)

“N/A” indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available. See Appendix B for additional information listed by drug.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>EIs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding Events</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>Spontaneous bleeding, hematuria in hemophilia</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TPV: Intracranial hemorrhage is associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, and the use of vitamin E supplements.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bone Density Effects</strong></td>
<td>TDF: Associated with greater loss of BMD than other NRTIs. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting.</td>
<td>TAF: Associated with smaller declines in BMD than those seen with TDF.</td>
<td>Decreases in BMD observed after the initiation of any ART regimen.</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Bone Marrow Suppression</strong></td>
<td>ZDV: Anemia, neutropenia</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Cardiac Conduction Effects</strong></td>
<td>N/A</td>
<td>RPV, EFV: QTc prolongation</td>
<td>SQV/r, ATV/r, and LPV/r: PR prolongation. Risk factors include pre-existing heart disease and the use of other medications. SQV/r: QT prolongation. Obtain ECG before administering SQV.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td>ABC and ddi: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.</td>
<td>N/A</td>
<td>DRV, FPV, IDV, and LPV/r: Associated with cardiovascular events in some cohorts</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Cholelithiasis</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 2 of 5)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>Pls</th>
<th>INSTIs</th>
<th>Els</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus and Insulin Resistance</td>
<td>ZDV, d4T, and ddI</td>
<td>N/A</td>
<td>Reported for some (IDV, LPV/r), but not all, Pls.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>d4T &gt; ZDV &gt; ABC: ↑ TG and LDL</td>
<td>TAF: ↑ TG, ↑ LDL, ↑ HDL (no change in TC:HDL ratio)</td>
<td>All RTV- or COBI-Boosted Pls: ↑ TG, ↑ LDL, ↑ HDL</td>
<td>EVG/c: ↑ TG, ↑ LDL, ↑ HDL</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TDF has been associated with lower lipid levels than ABC or TAF.</td>
<td></td>
<td>LPV/r and FPV/r &gt; DRV/r and ATV/r: ↑ TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Effects</td>
<td>ddI and ZDV &gt; Other NRTIs: Nausea and vomiting ddI: Pancreatitis</td>
<td>N/A</td>
<td>GI intolerance (e.g., diarrhea, nausea, vomiting)</td>
<td>EVG/c: Nausea and diarrhea</td>
<td>IBA: 8% of patients reported diarrhea in a study of 40 people.</td>
</tr>
<tr>
<td>Hepatic Effects</td>
<td>Reported with most NRTIs. ZDV, d4T, and ddI: Steatosis ddI: Prolonged exposure linked to noncirrhotic portal hypertension and esophageal varices. When TAF, TDF, 3TC, and FTC are Withdrawn in Patients with HBV/HIV Coinfection or When HBV Resistance Develops: Patients with HBV/HIV coinfection may develop severe hepatic flares.</td>
<td>EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts &gt;250 cells/mm³ and men with pre-NVP CD4 counts &gt;400 cells/mm³. NVP should never be used for post-exposure prophylaxis. EFV and NVP are not recommended in patients with hepatic insufficiency (Child-Pugh class B or C).</td>
<td>All Pls: Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency occurs with TPV/r. TPV/r: Contraindicated in patients with hepatic insufficiency (Child Pugh class B or C). IDV and ATV: Jaundice due to indirect hyperbilirubinemia</td>
<td>N/A</td>
<td>MVC: Hepatotoxicity with or without rash or HSRs reported.</td>
</tr>
</tbody>
</table>
Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 3 of 5)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>EIs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypersensitivity Reaction</strong> Excluding rash alone or Stevens-Johnson syndrome</td>
<td><strong>ABC</strong>: Contraindicated if patient is HLA-B<em>5701 positive. Median onset for HSR is 9 days; 90% of reactions occur within first 6 weeks of treatment. <strong>HSR Symptoms (in Order of Descending Frequency)</strong>: Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B</em>5701 status.</td>
<td><strong>NVP</strong>: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts &gt;250 cells/mm³ and men with pre-NVP CD4 counts &gt;400 cells/mm³. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.</td>
<td>N/A</td>
<td>RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in &lt;1% of patients in clinical development program.</td>
<td>MVC: HSR reported as part of a syndrome related to hepatotoxicity.</td>
</tr>
<tr>
<td><strong>Lactic Acidosis</strong> Reported with NRTIs. Especially d4T, ZDV, and ddI: Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate &gt;10 mmol/L. Women and obese patients at increased risk.</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Lipodystrophy</strong> Lipatrophy: d4T &gt; ZDV. More likely when NRTIs are coadministered with EFV than with an RTV-boosted PI.</td>
<td>Lipohypertrophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.</td>
<td>N/A</td>
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</table>
Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 4 of 5)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Drug Class</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>Els</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy/Elevated Creatine Phosphokinase</td>
<td>ZDV: Myopathy</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>RAL and DTG: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>d4T &gt; ddI: Peripheral neuropathy (can be irreversible)</td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nervous System/Psychiatric Effects</td>
<td>d4T: Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)</td>
<td>Neuropsychiatric Events: EFV &gt; RPV, DOR &gt; ETR</td>
<td></td>
<td>N/A</td>
<td>All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>FTC: Hyperpigmentation</td>
<td>All NNRTIs</td>
<td>ATV, DRV, FPV, LPV/r, and TPV</td>
<td>All INSTIs</td>
<td>MVC, IBA</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 5 of 5)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>Els</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Effects/Urolithiasis</strong></td>
<td>TDF: ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. TAF: Less impact on renal biomarkers and lower rates of proteinuria than TDF.</td>
<td>RPV: Inhibits Cr secretion without reducing renal glomerular function.</td>
<td>ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. IDV: ↑ SCr, pyuria, renal atrophy, or hydrenephrosis IDV, ATV: Stone or crystal formation. Adequate hydration may reduce risk. COBI (as a Boosting Agent for DRV or ATV): Inhibits Cr secretion without reducing renal glomerular function.</td>
<td>DTG, COBI (as a Boosting Agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function</td>
<td>IBA: SCr abnormalities ≥ Grade 3 reported in 10% of trial participants.</td>
</tr>
<tr>
<td><strong>Stevens-Johnson Syndrome/Toxic Epidermal Necrosis</strong></td>
<td>Some reported cases for ddI and ZDV. NVP &gt; DLV, EFV, ETR, RPV</td>
<td>Some reported cases for FPV, DRV, IDV, LPV/r, and ATV.</td>
<td>RAL</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ATG = atazanavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; Cr = creatinine; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nevirapine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine
Switching Antiretroviral Therapy Due to Adverse Effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART-associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening adverse events (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching from an effective ARV regimen (or agent) to a new regimen (or agent) must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that resistance mutations are archived in HIV reservoirs, regardless of when the mutations were identified by genotypic resistance testing. Even if resistance mutations are absent from subsequent resistance test results, they may reappear under selective drug pressure. It is critical that providers review the following information before implementing any treatment switch:

- The patient’s medical and complete ARV history, including prior virologic responses to ART;
- All previous resistance test results;
- Viral tropism (if MVC is being considered);
- HLA-B*5701 status (if ABC is being considered);
- Comorbidities;
- The patient’s pregnancy status, ability to use effective contraceptives, and desire for pregnancy (if DTG is being considered for patients of child-bearing potential);
- HBV status, since patients with evidence of chronic HBV infection should not discontinue TDF or TAF unless a regimen contains another agent that is active against HBV;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements, taking into consideration any potential drug interactions with ARVs.

A patient’s willingness to accept new requirements for food or dosing must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of comorbidities, adverse effects of concomitant medications, or HIV itself may mimic adverse effects caused by ART. Therefore, clinicians should investigate all potential causes for an adverse event. In the case of a severe adverse event, it may be necessary to discontinue or switch ARVs pending the outcome of such an investigation. For the first few months after an ART switch, the patient should be closely monitored for any new adverse events. The patient’s viral load should also be monitored to assure continued viral suppression.

Table 16 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.
Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent  (page 1 of 3)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s) or Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Density Effects</strong></td>
<td>TDF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.</td>
</tr>
<tr>
<td></td>
<td>TAF or ABC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bone Marrow Suppression</strong></td>
<td>ZDV</td>
<td>ZDV has been associated with neutropenia and macrocytic anemia.</td>
</tr>
<tr>
<td></td>
<td>TDF, TAF, or ABC&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac QTc Interval Prolongation</strong></td>
<td>EFV, RPV</td>
<td>High EFV and RPV exposures may cause QT prolongation. Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.</td>
</tr>
<tr>
<td></td>
<td>A PI- or INSTI-based regimen</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Events</strong></td>
<td>ABC</td>
<td>ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.</td>
</tr>
<tr>
<td><strong>Myocardial infarction, ischemic stroke</strong></td>
<td>RTV- or COBI-boosted PI</td>
<td>RAL, DTG, BIC, or RPV</td>
</tr>
<tr>
<td></td>
<td>regimens, EFV, EVG/c</td>
<td>RAL, DTG, BIC, and RPV have less effect on lipids than RTV- or COBI-boosted PI regimens, EFV, and EVG/c. Large observation cohorts have found an association between some PIs (DRV, FPV, IDV, LPV/r) and an increased risk of CV events. However, this association has not been seen with ATV. Further study is needed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central Nervous System, Neuropsychiatric Side Effects</strong></td>
<td>EFV, RPV</td>
<td>In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV. INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.</td>
</tr>
<tr>
<td></td>
<td>ETR, PI/c, or PI/r</td>
<td>INSTIs may be used, but monitoring is recommended (see Comments column).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>RTV- or COBI-boosted PI</td>
<td>Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia (with or without elevated LDL level)</strong></td>
<td>RTV- or COBI-boosted PI</td>
<td></td>
</tr>
</tbody>
</table>
Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent  (page 2 of 3)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s) or Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>ATM/c, ATV/r, DRV/c, DRV/r, RAL, DTG, BIC, or EVG/c</td>
</tr>
<tr>
<td>Other RTV- or COBI-boosted regimens</td>
<td>RAL, DTG, BIC, or NNRTIs</td>
<td>In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/ TDF/FTC and ATV/r plus TDF/FTC.</td>
</tr>
</tbody>
</table>

| Hypersensitivity Reaction | ABC | TDF or TAF | Never rechallenge with ABC following a suspected HSR, regardless of the patient’s HLA-B*5701 status. |
| | NVP, EFV, ETR, RPV | Non-NNRTI ART | Risk of HSR with NVP is higher for women and those with high CD4 cell counts. |
| | DTG, RAL | Non-INSTI ART | Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases. |

| Insulin Resistance | LPV/r, FPV/r | INSTI, NNRTI | Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than the use of any PI. |

| Jaundice and Icterus | ATV, ATM/c, ATV/r | DRV/c, DRV/r, INSTI, or NNRTI | Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient. |

| Lipoatrophy | d4T, ZDV | TDF, TAF, or ABC<sup>b</sup> | Peripheral lipatrophy is associated with prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipatrophy, but fat recovery is typically slow (may take years) and incomplete. |

| Lipohypertrophy | | | Accumulation of visceral, truncal, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse weight or visceral fat gain. |

| Rash | NNRTIs (especially NVP and EFV) | PI- or INSTI-based regimen | Mild rashes that develop after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class. |
| | DRV/c, DRV/r | ATM/c, ATV/r, or another drug class (e.g., INSTI) | Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class. |
| Table 16. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 3 of 3) |
|---|---|---|
| **Renal Effects** | **ARV Agent(s) or Drug Class** | **Comments** |
| Including proximal renal tubulopathy and elevated creatinine | TDF<sup>a</sup> | ABC, TAF (for patients with CrCl >30 mL/min), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate. |
| | | TDF may cause tubulopathy. Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting. |
| | ATV/c, ATV/r, LPV/r | DTG, BIC, RAL, or NNRTI |
| **Stones** | ATV, ATV/c, ATV/r | DRV/c, DRV/r, INSTI, or NNRTI |
| Nephrolithiasis and cholelithiasis | This switch should be made if the clinician believes ATV is the cause of the stones. |

<sup>a</sup> In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

<sup>b</sup> ABC should be used only in patients known to be HLA-B*5701 negative.

<sup>c</sup> TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CrCl = creatine clearance; CV = cardiovascular; d4T = stavudine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

**References**


Although antiretroviral therapy (ART) is expensive (see Table 16 below), the cost-effectiveness of ART has been demonstrated in analyses of older\(^1\) and newer regimens,\(^2,3\) as well as for treatment-experienced patients with drug-resistant HIV.\(^4\) Given the recommendations for immediate initiation of lifelong treatment and the increasing number of patients taking ART, the Panel now introduces cost-related issues pertaining to medication adherence and cost-containment strategies, as discussed below.

**Costs as They Relate to Adherence from a Patient Perspective**

**Cost sharing:** Cost sharing is where the patient is responsible for some of the medication cost burden (usually accomplished via copayments, coinsurance, or deductibles); these costs are often higher for branded medications than for generic medications. In one comprehensive review, increased patient cost sharing resulted in decreased medical adherence and more frequent drug discontinuation; for patients with chronic diseases, increased cost sharing was also associated with increased use of the medical system.\(^5\) Conversely, copayment reductions, such as those that might be used to incentivize prescribing of generic drugs, have been associated with improved adherence in patients with chronic diseases.\(^6\) Whereas cost sharing disproportionately affects low-income patients, resources (e.g., the Ryan White AIDS Drug Assistance Program [ADAP]) are available to assist eligible patients with copays and deductibles. Given the clear association between out-of-pocket costs for patients with chronic diseases and the ability of those patients to pay for and adhere to medications, clinicians should minimize patients’ out-of-pocket drug-related expenses whenever possible.

**Prior authorizations:** As a cost-containment strategy, some programs require that clinicians obtain prior authorizations or permission before prescribing newer or more costly treatments rather than older or less expensive drugs. Although there are data demonstrating that prior authorizations do reduce spending, several studies have also shown that prior authorizations result in fewer prescriptions filled and increased nonadherence.\(^7-9\) Prior authorizations in HIV care specifically have been reported to cost over $40 each in provider personnel time (a hidden cost) and have substantially reduced timely access to medications.\(^10\)

**Generic ART:** The impact of the availability of generic antiretroviral (ARV) drugs on selection of ART in the United States is unknown. Because U.S. patent laws currently limit the coformulation of some generic alternatives to branded drugs, generic options may result in increased pill burden. To the extent that pill burden, rather than drug frequency, results in reduced adherence, generic ART could lead to decreased costs but at the potential expense of worsening virologic suppression rates and poorer clinical outcomes.\(^11,12\) Furthermore, prescribing the individual, less-expensive generic components of a branded coformulated product rather than the branded product itself could, under some insurance plans, lead to higher copays—an out-of-pocket cost increase that may reduce medication adherence.

**Potential Cost Containment Strategies from a Societal Perspective**

Given resource constraints, it is important to maximize the use of resources without sacrificing clinical outcomes. Evidence-based revisions to these guidelines recommend tailored laboratory monitoring for patients with long-term virologic suppression on ART as one possible way to provide overall cost savings. Data suggest that continued CD4 monitoring yields no clinical benefit for patients whose viral loads are suppressed and whose CD4 counts exceed 200 cells/mm\(^3\) after 48 weeks of therapy.\(^13\) A reduction in laboratory use from biannual to annual CD4 monitoring could save ~$10 million per year in the United States\(^14\) (see Laboratory Monitoring). Although this is a small proportion of the overall costs associated with HIV care, such a strategy could reduce patients’ personal expenses if they have deductibles for laboratory tests. The present and future availability of generic formulations of certain ARV drugs, despite the potential caveats of increased pill burden and reduced adherence, offers other money-saving possibilities on a much
greater scale. One analysis suggests the possibility of saving approximately $900 million nationally in the first year of switching from a branded fixed-dose combination product to a three-pill regimen containing generic efavirenz.³

In summary, understanding HIV and ART related-costs in the United States is complicated because of the wide variability in medical coverage, accessibility, and expenses across regions, insurance plans, and pharmacies. In an effort to retain excellent clinical outcomes in an environment of cost-containment strategies, providers should remain informed of current insurance and payment structures, ART costs (see Table 16 below for estimates of drugs’ average wholesale prices), discounts among preferred pharmacies, and available generic ART options. Providers should work with patients and their case managers and social workers to understand their patients’ particular pharmacy benefit plans and potential financial barriers to filling their prescriptions. Additionally, providers should familiarize themselves with ARV affordability resources (such as ADAP and pharmaceutical company patient assistance programs for patients who qualify) and refer patients to such assistance if needed.
Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs *(Last updated November 26, 2018; last reviewed October 25, 2018)*

Prescription drug pricing in the United States involves complex systems of negotiations, rebates, discounts, and reimbursement rates. Much of the information used to determine drug prices is confidential, and prices can vary depending on the purchaser, the type of public or private insurance coverage in use, and the number of generic competitors. In addition, price increases that exceed rates of inflation can trigger additional rebates for Medicaid and 340B Drug Discount Program entities. Table 17 includes three benchmark prices, rounded to the nearest dollar, for commonly used antiretroviral (ARV) drugs as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact patients’ pharmacies or payors regarding actual prices, comparative cost savings, and related formulary restrictions.

**Wholesale acquisition cost (WAC)** is the list price published by manufacturers for prescription drugs or biologics sold to wholesalers. The WAC price approximates what retail pharmacies pay wholesalers for single-source (e.g., brand-name) drugs. There is a range of WAC prices for generic ARVs, as these are multiple-source products with variable list prices. With increasing competition, actual transactional prices of generic drugs among wholesalers and pharmacies decrease substantially. **Average wholesale price (AWP)** has historically been used as the basis for setting public (e.g., Medicaid) and private (e.g., commercial insurer) reimbursement rates for pharmacies. Neither WAC nor AWP include variable price concessions along supply and payment chains, including discounts and rebates to wholesalers, pharmacies, federal purchasers (e.g., the Veterans’ Administration), pharmacy benefit managers, commercial insurers, Medicaid, 340B pharmacies, and AIDS Drug Assistance Programs. The availability of these discounts and rebates depends on product demand, market competition, and WAC price increases set by manufacturers. Maximum prices are assigned to generic products with three or more therapeutically and pharmaceutically equivalent products, as determined by the Food and Drug Administration. This federally established price is the **federal upper limit (FUL)**. Federal Medicaid will reimburse state Medicaid programs up to this limit for multiple-source drugs (plus the dispensing fee); commercial insurers set their own reimbursement upper limits with pharmacies. Whereas WACs and AWPs are generally set annually, FULs are adjusted monthly, particularly for multiple-source drugs with fluctuating pharmacy acquisition costs. In the table below, the FUL for a drug is described as “pending” if a generic drug currently lacks the competition required to trigger a FUL.

<table>
<thead>
<tr>
<th>ARV Drug (Generic and Brand Names)</th>
<th>Tablets, Capsules, or mLs per Month</th>
<th>WAC (Monthly)b</th>
<th>AWP (Monthly)b</th>
<th>FUL (As of 9/1/2018)c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abacavir</strong></td>
<td>300 mg tablet</td>
<td>60 tablets</td>
<td>$150 to $482</td>
<td>$579 to $603</td>
</tr>
<tr>
<td>• Generic</td>
<td>300 mg tablet</td>
<td>60 tablets</td>
<td>$482</td>
<td>$579 to $603</td>
</tr>
<tr>
<td>• Ziagen</td>
<td>300 mg tablet</td>
<td>60 tablets</td>
<td>$559</td>
<td>$670</td>
</tr>
<tr>
<td><strong>Emtricitabine</strong></td>
<td>200 mg capsules</td>
<td>30 capsules</td>
<td>$537</td>
<td>$644</td>
</tr>
<tr>
<td>• Emtriva</td>
<td>300 mg tablet</td>
<td>30 tablets</td>
<td>$75 to $343</td>
<td>$429 to $430</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td>300 mg tablet</td>
<td>30 tablets</td>
<td>$416</td>
<td>$499</td>
</tr>
</tbody>
</table>
### Nucleoside Reverse Transcriptase Inhibitors (NRTIs), continued

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Strength, Formulation</th>
<th>Tablets, Capsules, or mLs per Month</th>
<th>WAC (Monthly)</th>
<th>AWP (Monthly)</th>
<th>FUL (As of 9/1/2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir Disoproxil Fumarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Generic</td>
<td>300 mg tablet</td>
<td>30 tablets</td>
<td>$58 to $922</td>
<td>$110 to $1,216</td>
<td>Pending</td>
</tr>
<tr>
<td>• Viread</td>
<td>300 mg tablet</td>
<td>30 tablets</td>
<td>$1,140</td>
<td>$1,368</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Generic</td>
<td>300 mg tablet</td>
<td>60 tablets</td>
<td>$36 to $54</td>
<td>$54 to $365</td>
<td>$13</td>
</tr>
</tbody>
</table>

### NRTI Combination Products

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Strength, Formulation</th>
<th>Tablets, Capsules, or mLs per Month</th>
<th>WAC (Monthly)</th>
<th>AWP (Monthly)</th>
<th>FUL (As of 9/1/2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/Lamivudine</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>• Generic</td>
<td>600 mg/300 mg tablets</td>
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<td>• Epzicom</td>
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<td>Tenofovir Alafenamide/Emtricitabine</td>
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</tr>
<tr>
<td>• Descovy</td>
<td>25 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$1,676</td>
<td>$2,011</td>
<td>N/A</td>
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<tr>
<td>Tenofovir Disoproxil Fumarate/Emtricitabine</td>
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<td></td>
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</tr>
<tr>
<td>• Truvada</td>
<td>300 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$1,676</td>
<td>$2,011</td>
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<tr>
<td>• Cimduo</td>
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<td>Zidovudine/Lamivudine</td>
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</tr>
<tr>
<td>• Generic</td>
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<td>• Combivir</td>
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<td>Abacavir Sulfate/Zidovudine/Lamivudine</td>
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<tr>
<td>• Generic</td>
<td>300 mg/300 mg/150 mg tablet</td>
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<td>• Trizivir</td>
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### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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<th>ARV Drug</th>
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<th>AWP (Monthly)</th>
<th>FUL (As of 9/1/2018)</th>
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<td>Efavirenz</td>
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<td>• Generic</td>
<td>600 mg tablet</td>
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</tr>
<tr>
<td>• Sustiva</td>
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<td>30 tablets</td>
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<td>Doravirine</td>
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<tr>
<td>• Pifeltro</td>
<td>100 mg tablet</td>
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<td>$1,380</td>
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<td>ARV Drug (Generic and Brand Names)</td>
<td>Strength, Formulation</td>
<td>Tablets, Capsules, or mLs per Month</td>
<td>WAC (Monthly)</td>
<td>AWP (Monthly)</td>
<td>FUL (As of 9/1/2018)</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<tr>
<td><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), continued</strong></td>
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<td>Etravirine</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intence</td>
<td>200 mg tablet</td>
<td>60 tablets</td>
<td>$1,296</td>
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<td>Nevirapine</td>
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<td>• Generic</td>
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<td>$10 to $45</td>
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<td>• Viramune</td>
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<td>$246 to $565</td>
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<td>• Viramune XR</td>
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<td>$951</td>
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<td>Rilpivirine</td>
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<tr>
<td>• Edurant</td>
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<td><strong>Protease Inhibitors (PIs)</strong></td>
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<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Generic</td>
<td>200 mg capsule</td>
<td>60 capsules</td>
<td>$878 to $1,264</td>
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</tr>
<tr>
<td>• Reyataz</td>
<td>200 mg capsule</td>
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<tr>
<td>• Generic</td>
<td>300 mg capsule</td>
<td>30 capsules</td>
<td>$870 to $1,252</td>
<td>$1,565 to $1,652</td>
<td>Pending</td>
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<tr>
<td>• Reyataz</td>
<td>300 mg capsule</td>
<td>30 capsules</td>
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<tr>
<td>Atazanavir/Cobicistat</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>• Evotaz</td>
<td>300/150 mg tablet</td>
<td>30 tablets</td>
<td>$1,605</td>
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<tr>
<td>Darunavir</td>
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<td></td>
</tr>
<tr>
<td>• Prezista</td>
<td>600 mg tablet</td>
<td>60 tablets</td>
<td>$1,581</td>
<td>$1,897</td>
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<td>• Prezista</td>
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<td>30 tablets</td>
<td>$1,581</td>
<td>$1,897</td>
<td>N/A</td>
</tr>
<tr>
<td>• Prezista</td>
<td>100 mg/mL suspension</td>
<td>200 mL</td>
<td>$878</td>
<td>$1,054</td>
<td>N/A</td>
</tr>
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<td>Darunavir/Cobicistat</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Prezobix</td>
<td>800 mg/150 mg tablet</td>
<td>30 tablets</td>
<td>$1,806</td>
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<tr>
<td>Lopinavir/Ritonavir</td>
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<td></td>
</tr>
<tr>
<td>• Kaletra</td>
<td>200 mg/50 mg tablet</td>
<td>120 tablets</td>
<td>$1,024</td>
<td>$1,229</td>
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<tr>
<td>Tipranavir</td>
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<tr>
<td>• Aptivus</td>
<td>250 mg capsule</td>
<td>120 capsules</td>
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<td>$1,894</td>
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### ARV Drug (Generic and Brand Names)

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<th>Integrase Strand Transfer Inhibitors (INSTIs)</th>
<th>Strength, Formulation</th>
<th>Tablets, Capsules, or mLS per Month</th>
<th>WAC (Monthly)</th>
<th>AWP (Monthly)</th>
<th>FUL (As of 9/1/2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dolutegravir</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Tivicay</td>
<td>50 mg tablet</td>
<td>30 tablets</td>
<td>$1,658</td>
<td>$1,989</td>
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<tr>
<td>• Tivicay</td>
<td>50 mg tablet</td>
<td>60 tablets</td>
<td>$3,315</td>
<td>$3,978</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Isentress</td>
<td>400 mg tablet</td>
<td>60 tablets</td>
<td>$1,500</td>
<td>$1,800</td>
<td>N/A</td>
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<tr>
<td>• Isentress HD</td>
<td>600 mg tablet</td>
<td>60 tablets</td>
<td>$1,500</td>
<td>$1,800</td>
<td>N/A</td>
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<tr>
<td><strong>Fusion Inhibitor</strong></td>
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<td></td>
<td></td>
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<td><strong>Enfuvirtide</strong></td>
<td></td>
<td></td>
<td></td>
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<td>• Fuzeon</td>
<td>90 mg injection kit</td>
<td>60 doses (1 kit)</td>
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<tr>
<td><strong>CCR5 Antagonist</strong></td>
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<tr>
<td><strong>Maraviroc</strong></td>
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<tr>
<td>• Selzentry</td>
<td>150 mg tablet</td>
<td>60 tablets</td>
<td>$1,511</td>
<td>$1,813</td>
<td>N/A</td>
</tr>
<tr>
<td>• Selzentry</td>
<td>300 mg tablet</td>
<td>60 tablets</td>
<td>$1,511</td>
<td>$1,813</td>
<td>N/A</td>
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<tr>
<td>• Selzentry</td>
<td>300 mg tablet</td>
<td>120 tablets</td>
<td>$3,022</td>
<td>$3,626</td>
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</tr>
<tr>
<td><strong>CD4-Directed Post-Attachment Inhibitor</strong></td>
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<tr>
<td><strong>Ibalizumab-uiyk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trogarzo</td>
<td>200 mg vials</td>
<td>8 vials</td>
<td>$9,080</td>
<td>$10,896</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Coformulated Combination Products as Single Tablet Regimens</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bictegravir/Tenofovir Alafenamide/Emtricitabine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Biktarvy</td>
<td>50 mg/25 mg/200 mg</td>
<td>30 tablets</td>
<td>$2,946</td>
<td>$3,535</td>
<td>N/A</td>
</tr>
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<td><strong>Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Symtuza</td>
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<td>$4,178</td>
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<td></td>
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<tr>
<td>• Triumeq</td>
<td>50 mg/600 mg/300 mg tablet</td>
<td>30 tablets</td>
<td>$2,805</td>
<td>$3,366</td>
<td>N/A</td>
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<tr>
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<td>• Juluca</td>
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<td>30 tablets</td>
<td>$2,579</td>
<td>$3,095</td>
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<tr>
<td>• Delstrigo</td>
<td>100 mg/300 mg/300 mg</td>
<td>30 tablets</td>
<td>$2,100</td>
<td>$2,520</td>
<td>N/A</td>
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</tbody>
</table>
Table 17. Monthly Average Prices of Commonly Used Antiretroviral Drugs *(Last updated November 26, 2018; last reviewed October 25, 2018)*
(page 5 of 5)

<table>
<thead>
<tr>
<th>ARV Drug (Generic and Brand Names)</th>
<th>Strength, Formulation</th>
<th>Tablets, Capsules, or mLS per Month</th>
<th>WAC (Monthly)b</th>
<th>AWP (Monthly)b</th>
<th>FUL (As of 9/1/2018)c</th>
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<tbody>
<tr>
<td>Coformulated Combination Products as Single Tablet Regimens, continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Atripla</td>
<td>600 mg/300 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$2,724</td>
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<td></td>
<td></td>
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<tr>
<td>• Symfi</td>
<td>600 mg/300 mg/150 mg tablet</td>
<td>30 tablets</td>
<td>$1,634</td>
<td>$1,961</td>
<td>N/A</td>
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<tr>
<td>• Symfi Lo</td>
<td>400 mg/300 mg/150 mg tablet</td>
<td>30 tablets</td>
<td>$1,634</td>
<td>$1,961</td>
<td>N/A</td>
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<tr>
<td>Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine</td>
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<td></td>
</tr>
<tr>
<td>• Genvoya</td>
<td>150 mg/150 mg/10 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$2,946</td>
<td>$3,535</td>
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<td>Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine</td>
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<td>• Strivid</td>
<td>150 mg/150 mg/300 mg/200 mg tablet</td>
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<tr>
<td>• Odelixy</td>
<td>25 mg/25 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$2,681</td>
<td>$3,217</td>
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<td>Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine</td>
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<td></td>
<td></td>
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<tr>
<td>• Complera</td>
<td>25 mg/300 mg/200 mg tablet</td>
<td>30 tablets</td>
<td>$2,681</td>
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<td>N/A</td>
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<tr>
<td>Pharmacokinetic Enhancers (Boosters)</td>
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<td>Cobicistat</td>
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<td>• Tybost</td>
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<td>$219</td>
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<td>• Generic</td>
<td>100 mg tablet</td>
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<td>• Norvir</td>
<td>100 mg tablet</td>
<td>30 tablets</td>
<td>$257</td>
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</tbody>
</table>

* The following less commonly used ARV drugs are not included in this table: delavirdine, didanosine, fosamprenavir, indinavir, nelfinavir, saquinavir, and stavudine.


References


Drug-Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018)

Pharmacokinetic (PK) drug-drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug-drug interactions—both those affecting ARVs and those affecting the other drugs a patient is taking. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common mechanisms of interactions are described below and listed for each ARV drug in Table 18.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents, such as proton pump inhibitors, H2 antagonists, or antacids, can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir [ATV] and rilpivirine [RPV]).

- Products that contain polyvalent cations, such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium, can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.

- Drugs that induce or inhibit the enzyme cytochrome P450 3A4 (CYP3A4) or efflux transporter p-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions.

- The cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), the CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.

- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs dolutegravir (DTG) and raltegravir (RAL). Drugs that induce or inhibit the UGT enzyme can affect the PKs of these INSTIs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir
(RTV) and cobicistat (COBI). Both of these drugs are potent inhibitors of the CYP3A4 enzyme, resulting in higher systemic exposures of the coadministered ARV that is metabolized by this pathway. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

**Other Mechanisms of Pharmacokinetic Interactions**

Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters.

Tables 19a through 20b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modifications or alternative therapy.

**Role of Therapeutic Drug Monitoring in Managing Drug-Drug Interactions**

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important PK drug-drug interaction, the first step is to assess whether there are other, equally effective treatment options that can be used in order to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Assays for some ARV drug concentrations are commercially available; however, it may take 1 week or longer for the results to be reported. When interpreting the results, clinicians should take into account the patient’s medication adherence, the timing of last dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, it is necessary to repeat TDM after the adjusted drug reaches steady state in order to assure appropriate dosing.

TDM information should not be used alone; it must be integrated with other clinical information, including virologic responses and signs and symptoms of drug toxicities, to assure safe and effective therapy.
Table 18. Mechanisms of Antiretroviral-Associated Drug Interactions  (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

**Note:** N/A indicates that there are no clinically relevant interactions by these mechanisms. Identified mechanisms are specific to individual ARV drugs and not combinations of ARV drugs.

<table>
<thead>
<tr>
<th>ARV Drugs by Drug Class</th>
<th>Mechanisms That May Affect Oral Absorption of ARV Drugs</th>
<th>Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs</th>
<th>UGT1A1</th>
<th>Other Mechanisms of Known Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasing Gastric pH</td>
<td>Cationic Chelation</td>
<td>P-glycoprotein</td>
<td>CYP Substrate</td>
</tr>
<tr>
<td>INSTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Enhancers (Boosters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COBI</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate, inhibitor</td>
</tr>
<tr>
<td>RTV</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate, inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV</td>
<td>Concentration decreased</td>
<td>N/A</td>
<td>Substrate, inhibitor</td>
<td>3A4, 2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate, inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPV</td>
<td>Concentration decreased by H2 antagonist</td>
<td>N/A</td>
<td>Substrate, inhibitor</td>
<td>3A4, 2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td>SQA</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>N/A</td>
<td></td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td>EFV</td>
<td>N/A</td>
<td></td>
<td></td>
<td>2B6 (primary), 2A6, 3A4</td>
</tr>
</tbody>
</table>
### Table 18. Mechanisms of Antiretroviral-Associated Drug Interactions

(As of October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

<table>
<thead>
<tr>
<th>ARV Drugs by Drug Class</th>
<th>Mechanisms That May Affect Oral Absorption of ARV Drugs</th>
<th>Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs</th>
<th>Other Mechanisms of Known Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasing Gastric pH</td>
<td>Cationic Chelation</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>NNRTIs, continued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETR</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>NVP</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>RPV</td>
<td>Concentration decreased</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>FTC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3TC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TAF</td>
<td>N/A</td>
<td>N/A</td>
<td>Substrate</td>
</tr>
<tr>
<td>TDF</td>
<td>N/A</td>
<td>N/A</td>
<td>Substrate</td>
</tr>
<tr>
<td>ZDV</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CCR5 Antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVC</td>
<td>N/A</td>
<td>N/A</td>
<td>Substrate</td>
</tr>
<tr>
<td>Fusion Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-20</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; Ca = calcium; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; Fe = iron; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; OCT2 = organic cation transporter 2; OATP = organic anion-transporting polypeptide; PK = pharmacokinetic; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase; ZDV = zidovudine; Zn = zinc
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  (Last updated October 25, 2018; last reviewed October 25, 2018)  (page 1 of 19)

This table provides known or predicted information regarding PK interactions between PIs and non-ARV drugs. When information is available, interactions for PK-boosted (with either RTV or COBI) and unboosted ATV are listed separately. The term “All PIs” refers to both unboosted ATV and PIs boosted with either RTV or COBI, except the PIs noted below. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a, and 20b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

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

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>All PIs</td>
<td>↑ alfuzosin expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>All PIs</td>
<td>↑ doxazosin possible</td>
<td>Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>All PIs</td>
<td>↑ tamsulosin expected</td>
<td>Coadministration is not recommended. If coadministered, monitor for tamsulosin toxicities.</td>
</tr>
<tr>
<td>Terazosin</td>
<td>All PIs</td>
<td>↔ or ↑ terazosin possible</td>
<td>Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.</td>
</tr>
<tr>
<td>Silodosin</td>
<td>All PIs</td>
<td>↑ silodosin expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td><strong>Acid Reducers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>ATP, ATV/c, ATV/r</td>
<td>When given simultaneously, ↓ ATV expected</td>
<td>Give ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>TPV AUC ↓ 27%</td>
<td>Give TPV at least 2 hours before or 1 hour after antacids.</td>
</tr>
<tr>
<td>H2 Receptor Antagonists</td>
<td>ATV (unboosted)</td>
<td>↓ ATV</td>
<td>H2 receptor antagonist single dose should not exceed a dose equivalent to famotidine 20 mg, and the total daily dose should not exceed a dose equivalent to famotidine 20 mg BID in PI-naive patients. Unboosted ATV plus famotidine should not be used in combination in PI-experienced patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.</td>
</tr>
<tr>
<td>ATVC, ATV/r</td>
<td>↓ ATV</td>
<td>H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or famotidine 20 mg BID in ART-experienced patients. Give ATV 300 mg plus (COBI 150 mg or RTV 100 mg) simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg plus (COBI 150 mg or RTV 100 mg).</td>
<td></td>
</tr>
<tr>
<td>DRV/c, DRV/r, LPV/r</td>
<td>↔ demonstrated or expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
</tbody>
</table>
Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
--- | --- | --- | --- |
**Acid Reducers, continued** |
**PPIs** |
ATV (unboosted) | ↓ ATV | PPIs are not recommended in patients receiving unboosted ATV. In these patients, consider alternative acid-reducing agents, RTV or COBI boosting, or alternative PIs.
ATV/c, ATV/r | ↓ ATV | PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients.
ATV/r | | PPIs should be administered at least 12 hours before ATV/c or ATV/r.
DRV/c, LPV/r | ↔ expected | No dose adjustment necessary.
DRV/r | Omeprazole AUC ↓ 42% | No dose adjustment necessary. If there is a lack of symptomatic relief, increase dose to no more than omeprazole 40 mg daily.
TPV/r | Omeprazole AUC ↓ 70% | Coadministration is not recommended. If coadministration is necessary, dose increases of omeprazole may be considered based on clinical response.

**Anticoagulants and Antiplatelets** |
**Apixaban** |
PI/c, PI/r | ↑ apixaban expected | Coadministration is not recommended in patients who require apixaban 2.5 mg twice daily.
In patients who require apixaban 5 mg or 10 mg twice daily, reduce apixaban dose by 50%.

**Betrixaban** |
ATV/c, ATV/r, LPV/r | ↑ betrixaban expected | Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.

**Dabigatran** |
ATV/c, ATV/r, LPV/r | ↑ dabigatran expected | Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran dosing instructions for concomitant use with P-gp inhibitors in dabigatran prescribing information.
With COBI 150 mg Alone:
• Dabigatran AUC ↑ 110% to 127%

**Edoxaban** |
ATV/c, ATV/r, LPV/r | ↑ edoxaban expected | Stroke Prevention in Nonvalvular Atrial Fibrillation Indication:
• No dose adjustment necessary.
Deep Venous Thrombosis and Pulmonary Embolism Indication:
• Administer edoxaban 30 mg once daily

**Rivaroxaban** |
PI/c, PI/r | ↑ rivaroxaban expected | Coadministration is not recommended.

**Ticagrelor** |
All PIs | ↑ ticagrelor expected | Coadministration is not recommended.

**Vorapaxar** |
All PIs | ↑ vorapaxar expected | Coadministration is not recommended.
## Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs

(Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI/r</td>
<td>↓ warfarin possible</td>
<td>Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV’s effect on warfarin.</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulants and Antiplatelets, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV (unboosted)</td>
<td>May ↓ PI levels substantially</td>
<td>Do not coadminister. Consider alternative anticonvulsant or ARV.</td>
<td></td>
</tr>
<tr>
<td>ATV/r, LPV/r, TPV/r</td>
<td>↑ carbamazepine possible</td>
<td>Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPV/r ↑ carbamazepine AUC 26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May ↓ PI levels substantially</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>Carbamazepine AUC ↑ 45%</td>
<td>Monitor anticonvulsant level and adjust dose accordingly.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV: no significant change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI/c</td>
<td>↑ carbamazepine possible</td>
<td>Contraindicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ cobicistat expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ PI levels expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eslicarbazepine, Oxcarbazepine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PIs</td>
<td>↓ PI possible</td>
<td>Consider alternative anticonvulsant or ARV. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentration.</td>
<td></td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All PIs</td>
<td>↑ ethosuximide possible</td>
<td>Clinically monitor for ethosuximide toxicities.</td>
<td></td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV (unboosted)</td>
<td>Lamotrigine: no effect</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>Lamotrigine AUC ↓ 32%</td>
<td>A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>Lamotrigine AUC ↓ 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV: no significant change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r, TPV/r</td>
<td>Lamotrigine possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI/c</td>
<td>No data</td>
<td>Monitor anticonvulsant level and adjust dose accordingly.</td>
<td></td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI/c</td>
<td>↓ cobicistat expected</td>
<td>Contraindicated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ PI levels expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV (unboosted), PI/r</td>
<td>May ↓ PI levels substantially</td>
<td>Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily or unboosted ATV.</td>
<td></td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 4 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenytoin</strong></td>
<td>ATV (unboosted)</td>
<td>May ↓ PI levels substantially</td>
<td><strong>Do not coadminister.</strong> Consider alternative anticonvulsant or ATV/r.</td>
</tr>
<tr>
<td></td>
<td>ATV/r, DRV/r, TPV/r</td>
<td>↓ phenytoin possible</td>
<td>Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Phenytoin AUC ↓ 31%</td>
<td>Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LPV/r AUC ↓ 33%</td>
<td><strong>Do not coadminister with LPV/r once daily.</strong></td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>↓ cobicistat expected</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>

| **Valproic Acid** (VPA) | PI/c, PI/r | ↓ or ↔VPA possible | Monitor VPA levels and virologic response. Monitor for LPV-related toxicities. |
|                        | LPV/r AUC ↑ 75% | | |

**Anticonvulsants, continued**

<table>
<thead>
<tr>
<th><strong>Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aripiprazole</strong></td>
</tr>
<tr>
<td>PI/c, PI/r</td>
</tr>
<tr>
<td>↑ aripiprazole expected</td>
</tr>
<tr>
<td>Administer 25% of the usual aripiprazole dose. Titrated based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.</td>
</tr>
<tr>
<td>ATV (unboosted)</td>
</tr>
<tr>
<td>↑ aripiprazole expected</td>
</tr>
<tr>
<td>Administer 50% of the usual aripiprazole dose. Titrated based on clinical monitoring for efficacy/toxicity. Refer to aripiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers.</td>
</tr>
</tbody>
</table>

| **Brexpiprazole**                                                                                |
| PI/c, PI/r                                                                                       |
| ↑ brexpiprazole expected                                                                        |
| Administer 25% of the usual brexpiprazole dose. Titrated based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers. |
| ATV (unboosted)                                                                                 |
| ↑ brexpiprazole expected                                                                        |
| Administer 50% of the usual brexpiprazole dose. Titrated based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for doses to use in patients who have major depressive disorder or who are known to be CYP2D6 poor metabolizers. |

| **Bupropion**                                                                                   |
| LPV/r                                                                                           |
| Bupropion AUC ↓ 57%                                                                            |
| Titrated bupropion dose based on clinical response.                                            |
| TPV/r                                                                                           |
| Bupropion AUC ↓ 46%                                                                            |
| ATP/r, DRV/r                                                                                    |
| ↓ bupropion possible                                                                           |
| No dose adjustment necessary.                                                                   |
| PI/c                                                                                           |
| ↔ bupropion expected                                                                           |

| **Buspirone**                                                                                   |
| All PIs                                                                                        |
| ↑ buspirone expected                                                                            |
| Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response. |
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 5 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cariprazine</td>
<td>All PIs</td>
<td>↑ cariprazine expected</td>
<td>Starting Cariprazine in a Patient Already Receiving a PI: • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of cariprazine 3 mg daily. If the PI is withdrawn, cariprazine dose may need to be increased.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Starting a PI in a Patient Already Receiving Cariprazine: • For patients receiving cariprazine 3 mg or cariprazine 6 mg daily, reduce dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to cariprazine 1.5 mg or cariprazine 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to cariprazine 1.5 mg every other day. If PI is withdrawn, cariprazine dose may need to be increased.</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>All PIs</td>
<td>↑ fluvoxamine possible</td>
<td>Titrate fluvoxamine dose based on clinical response.</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>PI/c, PI/r</td>
<td>↑ lurasidone expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>ATV (unboosted)</td>
<td></td>
<td>Consider alternative therapy. If coadministration is necessary, reduce lurasidone dose by 50%.</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>All PIs</td>
<td>↑ pimavanserin expected</td>
<td>Reduce dose from pimavanserin 34 mg daily to pimavanserin 17 mg daily.</td>
</tr>
<tr>
<td>Pimozide</td>
<td>All PIs</td>
<td>↑ pimozide expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>All PIs</td>
<td>↑ quetiapine expected</td>
<td>Starting Quetiapine in a Patient Receiving a PI: • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Starting a PI in a Patient Receiving a Stable Dose of Quetiapine: • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.</td>
</tr>
<tr>
<td>Trazodone</td>
<td>All PIs</td>
<td>RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%</td>
<td>Use lowest dose of trazodone and monitor for CNS and CV adverse effects.</td>
</tr>
<tr>
<td>Tricyclic Antidepressants (TCA)</td>
<td>All PIs</td>
<td>↑ TCA expected</td>
<td>Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.</td>
</tr>
<tr>
<td>Amitriptyline, desipramine, doxepin, imipramine, nor triptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Antipsychotics (CYP3A4 and/or CYP2D6 substrates)</td>
<td>PI/c, PI/r</td>
<td>↑ antipsychotic possible</td>
<td>Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.</td>
</tr>
<tr>
<td>Other Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)</td>
<td>DRV/r</td>
<td>Paroxetine AUC ↓ 39%</td>
<td>Titrate SSRI dose based on clinical response.</td>
</tr>
<tr>
<td></td>
<td>ATV/r, LPV/r, TPV/r, PI/c</td>
<td>Sertraline AUC ↓ 49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effects unknown</td>
<td>Titrate SSRI dose using the lowest available initial or maintenance dose.</td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  (Last updated October 25, 2018; last reviewed October 25, 2018)  (page 6 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>PI/c, ATV/r, DRV/r, LPV/r</td>
<td>No significant effect observed or expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>TPV AUC ↑ 50%</td>
<td>Fluconazole &gt;200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV.</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>LPV/r</td>
<td>Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%</td>
<td>If coadministered, consider monitoring isavuconazole concentrations and toxicities and assessing virologic response.</td>
</tr>
<tr>
<td></td>
<td>All PIs except LPV/r</td>
<td>↑ isavuconazole possible ↑ or ↓ PI possible</td>
<td>If coadministered, consider monitoring isavuconazole concentrations and toxicities. Monitor for PI toxicity and virologic response.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>All PIs</td>
<td>↑ itraconazole possible ↑ PI possible</td>
<td>Consider monitoring itraconazole level to guide dose adjustments. Doses &gt;200 mg/day are not recommended with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>ATV/r</td>
<td>ATV AUC ↑ 146% ↑ posaconazole possible</td>
<td>If coadministered, monitor for PI adverse effects. Consider monitoring for posaconazole concentrations and toxicities.</td>
</tr>
<tr>
<td></td>
<td>ATV</td>
<td>ATV AUC ↑ 268% ↑ posaconazole possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/c, DRV/c, DRV/r, LPV/r, TPV/r</td>
<td>↑ PI possible ↑ posaconazole possible</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>ATV (unboosted)</td>
<td>↑ voriconazole possible ↑ PI possible</td>
<td>Monitor for toxicities.</td>
</tr>
<tr>
<td></td>
<td>All PI/r</td>
<td>RTV 100 mg BID ↓ voriconazole AUC 39%</td>
<td>Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk. If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>Effect on voriconazole unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Antihyperglycemics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>PI/r</td>
<td>↓ canagliflozin expected</td>
<td>If a patient is already tolerating canagliflozin 100 mg daily, has an eGFR &gt;60 mL/min/1.73m², and requires additional glycemic control, consider increasing dose to canagliflozin 300 mg daily.</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>↓ canagliflozin possible</td>
<td>If used in combination, monitor glycemic control.</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>All PIs</td>
<td>↑ saxagliptin expected</td>
<td>Limit saxagliptin dose to 2.5 mg once daily.</td>
</tr>
<tr>
<td>Dapagliflozin/Saxagliptin</td>
<td>All PIs</td>
<td>↑ saxagliptin expected</td>
<td>Do not coadminister, as this coformulated drug contains 5 mg of saxagliptin.</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemether/Lumefantrine</td>
<td>DRV/r</td>
<td>Artemether AUC ↓ 16% DHA AUC ↓ 18% Lumefantrine AUC ↑ 2.5-fold</td>
<td>Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.</td>
</tr>
<tr>
<td></td>
<td>DRV/c</td>
<td>↑ lumefantrine expected Effect on artemether unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Artemether AUC ↓ 40% DHA AUC ↓ 17% Lumefantrine AUC ↑ 470%</td>
<td></td>
</tr>
<tr>
<td>Concomitant Drug</td>
<td>PI</td>
<td>Effect on PI and/or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>------------------</td>
<td>----</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Antimalarials, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Artesunate/ Mefloquine** | LPV/r | Dihydroartemisinin AUC ↓ 49%  
Mefloquine AUC ↓ 28%  
↔ LPV | Clinical significance unknown. If used, monitor closely for antimalarial efficacy. |
| **Atovaquone/ Proguanil** | ATV/r, LPV/r | With ATV/r:  
• Atovaquone AUC ↓ 46%  
• Proguanil AUC ↓ 41%  
With LPV/r:  
• Atovaquone AUC ↓ 74%  
• Proguanil AUC ↓ 38% | No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible. |
| **Mefloquine** | RTV | With RTV 200 mg BID:  
• RTV AUC ↓ 31%, C\text{\textsubscript{min}} ↓ 43%  
↔ mefloquine | Use with caution. Effect on exposure of RTV-boosted PIs is unknown. |
| **Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections)** |    |                                                 |                                             |
| **Bedaquiline** | All PIs | With LPV/r:  
• Bedaquiline AUC ↑ 1.9-fold  
With Other PI/r, ATV/c, or DRV/c:  
• ↑ bedaquiline possible | Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests. |
| **Clarithromycin** | ATV (unboosted) | Clarithromycin AUC ↑ 94%  
↑ clarithromycin expected  
DRV/r ↑ clarithromycin AUC 57%  
LPV/r ↑ clarithromycin expected  
RTV 500 mg BID ↑ clarithromycin 77%  
TPV/r ↑ clarithromycin 19%  
Clarithromycin ↑ TPV 66% | May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).  
Consider alternative macrolide (e.g., azithromycin).  
Monitor for clarithromycin-related toxicities or consider an alternative macrolide (e.g., azithromycin).  
Reduce clarithromycin dose by 50% in patients with CrCl 30−60 mL/min.  
Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min. |
<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimycobacterials (for treatment of <em>Mycobacterium tuberculosis</em> and nontuberculosis mycobacterial infections), continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>ATV (unboosted)</td>
<td>Rifabutin AUC expected</td>
<td>Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in patients with HIV than in healthy study participants.</td>
</tr>
<tr>
<td></td>
<td>ATV/r</td>
<td>Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r; Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r; Rifabutin AUC ↔ and metabolite AUC ↑ 881%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Compared with Rifabutin (300 mg daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r; Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>Rifabutin expected</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>All PIs</td>
<td>PI concentration by &gt;75%</td>
<td>Contraindicated. Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>All PIs</td>
<td>PI expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td><strong>Antipneumocystis and Antitoxoplasmosis Drug</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>ATV/r</td>
<td>↔ atovaquone</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Cardiac Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>TPV/r</td>
<td>Both amiodarone and PI possible</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>All PIs except TPV/r</td>
<td>Both amiodarone and PI possible</td>
<td>Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug levels.</td>
</tr>
<tr>
<td>Antiarhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)</td>
<td>ATV (unboosted)</td>
<td>Antiarrhythmic possible</td>
<td>Consider alternative antiarrhythmics or ARV. If coadministered, monitor for antiarrhythmic toxicities.</td>
</tr>
<tr>
<td></td>
<td>PI/c, PI/r</td>
<td>Antiarrhythmic possible</td>
<td>Do not coadminister. Consider alternative antiarrhythmics or ARV.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>ATV (unboosted)</td>
<td>Dronedarone possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>PI/c, PI/r</td>
<td>Dronedarone expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Flecanide</td>
<td>All PIs except TPV/r</td>
<td>Flecainide possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>Flecainide expected</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 9 of 19)

<table>
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<th>Effect on PI and/or Concomitant Drug Concentrations</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Medications, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>All PIs except TPV/r</td>
<td>↑ propafenone possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>↑ propafenone expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Quinidine</td>
<td>All PIs except TPV/r</td>
<td>↑ quinidine possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>↑ quinidine expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Beta-Blockers (e.g., carvedilol, metoprolol, timolol)</td>
<td>All PIs</td>
<td>↑ beta-blockers possible</td>
<td>May need to decrease beta-blocker dose; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).</td>
</tr>
<tr>
<td>Bosentan</td>
<td>All PIs</td>
<td>LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected</td>
<td>Do not coadminister bosentan and unboosted ATV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In Patients on a PI (Other than Unboosted ATV) &gt;10 Days:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Start bosentan at 62.5 mg once daily or every other day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In Patients on Bosentan who Require a PI (Other than Unboosted ATV):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stop bosentan ≥36 hours before PI initiation and restart bosentan 10 days after PI initiation at 62.5 mg once daily or every other day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>When Switching Between COBI and RTV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Maintain same bosentan dose.</td>
</tr>
<tr>
<td>Calcium Channel Blockers (CCBs), Except Diltiazem</td>
<td>All PIs</td>
<td>↑ dihydropyridine possible ↑ verapamil possible</td>
<td>Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB is used with ATV.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>PI/c, PI/r</td>
<td>RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin Cmax 41% and ↔ AUC</td>
<td>Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>ATV/c, ATV/r, ATV (unboosted)</td>
<td>Unboosted ATV ↑ diltiazem AUC 125% Greater ↑ likely with ATV/c or ATV/r</td>
<td>Decrease diltiazem dose by 50%. ECG monitoring is recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use with caution. Adjust diltiazem according to clinical response and toxicities.</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>PI/c, PI/r</td>
<td>↑ eplerenone expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>ATV (unboosted)</td>
<td>↑ ranolazine possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>PI/c, PI/r</td>
<td>↑ ranolazine expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>All PIs</td>
<td>↑ ivabradine expected</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone Inhaled or intranasal</td>
<td>DRV/r</td>
<td>↔ 17-BMP (active metabolite) AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTV 100 mg BID ↑ 17-BMP AUC 2-fold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All PIs except DRV/r</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal</td>
<td>All PIs</td>
<td>↑ glucocorticoids possible</td>
<td>Coadministration can result in adrenal insufficiency and Cushing’s syndrome. <strong>Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of adverse effects associated with corticosteroids.</strong> Consider an alternative corticosteroid (e.g., beclomethasone).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ PI possible</td>
<td></td>
</tr>
<tr>
<td>Betamethasone, Budesonide Systemic</td>
<td>All PIs</td>
<td>↑ glucocorticoids possible</td>
<td>Coadministration can result in adrenal insufficiency and Cushing’s syndrome. <strong>Do not coadminister unless potential benefits of systemic corticosteroid outweigh the risks of adverse effects associated with systemic corticosteroids.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ PI possible</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone Systemic</td>
<td>All PIs</td>
<td>↑ glucocorticoids possible</td>
<td>Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.</td>
</tr>
<tr>
<td>Prednisone, Prednisolone Systemic</td>
<td>LPV/r</td>
<td>↑ prednisolone AUC 31%</td>
<td>Coadministration may be considered if the potential benefits outweigh the risks of adverse effects associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing’s syndrome, and other corticosteroid-associated toxicities.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>↑ prednisolone possible</td>
<td></td>
</tr>
<tr>
<td>Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital</td>
<td>All PIs</td>
<td>↑ glucocorticoids expected</td>
<td><strong>Do not coadminister.</strong> Coadministration can result in adrenal insufficiency and Cushing’s syndrome.</td>
</tr>
</tbody>
</table>

**Hepatitis C Direct-Acting Antiviral Agents**

| Daclatasvir | ATV/ c, ATV/r | ↑ daclatasvir | Decrease daclatasvir dose to 30 mg once daily. |
| | | ↔ daclatasvir | No dose adjustment necessary. |
| | ATV (unboosted), DRV/c, DRV/r, LPV/r | No data | No dosing recommendations available at this time. |

| Dasabuvir plus Paritaprevir/Ombitasvir/RTV | ATV (unboosted) | ↔ ATV | ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir plus paritaprevir/ombitasvir/RTV. |
| | | | **Do not coadminister.** |
| | DRV | DRV C_{min} ↓ 43% to 48% | |
| | LPV/r | Paritaprevir AUC ↑ 117% | **Do not coadminister.** |
| | ATV/c, DRV/c, TPV/r | No data | **Do not coadminister.** |
### Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 11 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
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<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C Direct-Acting Antiviral Agents, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Elbasvir/Grazoprevir | ATV/r | Elbasvir AUC ↑ 4.8-fold  
Grazoprevir AUC ↑ 10.6-fold  
ATV ↔ by elbasvir  
ATV AUC ↑ 43% by grazoprevir | Contraindicated.  
May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. |
| | DRV/r | Elbasvir AUC ↑ 66%  
Grazoprevir AUC ↑ 7.5-fold  
↔ DRV | |
| | LPV/r | Elbasvir AUC ↑ 3.7-fold  
Grazoprevir AUC ↑ 12.9-fold  
↔ LPV | |
| | ATV (unboosted), ATV/c, DRV/c, TPV/r | ↑ grazoprevir expected | |
| Glecaprevir/Pibrentasvir | ATV (unboosted), ATV/c, ATV/r | When Given with ATV/r 300/100 mg Once Daily:  
• Glecaprevir AUC ↑ 6.5-fold  
• Pibrentasvir AUC ↑ 64% | Contraindicated. |
| | DRV/c, DRV/r | When Given with DRV/r 800/100 mg Once Daily:  
• Glecaprevir AUC ↑ 5-fold  
• ↔ pibrentasvir | Do not coadminister. |
| | LPV/r | Glecaprevir AUC ↑ 4-fold  
Pibrentasvir ↑ 2.5-fold | Do not coadminister. |
| | TPV/r | ↑ glecaprevir and pibrentasvir expected | Do not coadminister. |
| Ledipasvir/Sofosbuvir | ATV/r | ATV AUC ↑ 33%  
Ledipasvir AUC ↑ 113%  
↔ sofosbuvir | No dose adjustment necessary.  
Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions. |
| | DRV/r | ↔ DRV expected  
↔ ledipasvir/sofosbuvir  
↔ expected | |
| | ATV (unboosted), ATV/c, DRV/c, LPV/r | ↓ ledipasvir and sofosbuvir expected | Do not coadminister. |
| | TPV/r | | |
### Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 12 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C Direct-Acting Antiviral Agents, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>All PIs</td>
<td>Compared with Simeprevir 150 mg Alone, Simeprevir 50 mg plus DRV/r 800 mg/100 mg Daily: • Simeprevir AUC ↑ 159% RTV 100 mg BID ↑ simeprevir AUC 618%</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>TPV/r</td>
<td>↓ sofosbuvir expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td><strong>Sofosbuvir/ Velpatasvir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP/r</td>
<td>↔ ATP/r</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↔ sofosbuvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Velpatasvir AUC ↑ 2.4-fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>↔ DRV/r</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir AUC ↓ 28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↔ velpatasvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV (unboosted), ATV/c, DRV/c, LPV/r</td>
<td>↔ sofosbuvir and velpatasvir expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>TPV/r</td>
<td>↓ sofosbuvir expected</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ velpatasvir expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sofosbuvir/ Velpatasvir/ Voxilaprevir</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP (unboosted), ATV/c, ATV/r</td>
<td>When Given with ATV/r: • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>↑ voxilaprevir expected</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td>DRV/c , DRV/r</td>
<td>When Given with DRV/r: • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No dose adjustment needed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPV/r</td>
<td>↓ sofosbuvir expected</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ velpatasvir expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effect on voxilaprevir is unknown.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Herbal Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>All PIs</td>
<td>↓ PI expected</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 13 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal Contraceptives Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV (unboosted)</td>
<td>Ethinyl estradiol AUC ↑ 48%</td>
<td>Norethindrone AUC ↑ 110%</td>
<td>Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol(^b) or recommend alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Ethinyl estradiol AUC ↓ 19% and C(_{\text{min}}) ↓ 37%</td>
<td>Norgestimate ↑ 85%</td>
<td>Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.(^c) Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.</td>
</tr>
<tr>
<td>ATV/c</td>
<td>Drosperone AUC ↑ 2.3-fold</td>
<td>Ethinyl estradiol AUC ↓ 22%</td>
<td>Contraindicated with drosperone-containing hormonal contraceptive due to potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV drug.</td>
</tr>
<tr>
<td>DRV/c</td>
<td>Drosperone AUC ↑ 1.6-fold</td>
<td>Ethinyl estradiol AUC ↓ 30%</td>
<td>Clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV.</td>
</tr>
<tr>
<td>DRV/r, LPV/r, TPV/r</td>
<td>Ethinyl estradiol AUC ↓ 37% to 55%</td>
<td>Norethindrone AUC ↓ 14% to 34%</td>
<td>With TPV/r: (\leftrightarrow) norethindrone AUC Consider alternative or additional contraceptive method or alternative ARV drug.</td>
</tr>
<tr>
<td>Depot MPA Injectable</td>
<td>LPV/r</td>
<td>MPA AUC ↑ 46%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>All other PIs</td>
<td>Etonogestrel AUC ↑ 52% and C(_{\text{min}}) ↑ 34%</td>
<td>Use standard dose.</td>
<td></td>
</tr>
<tr>
<td>Etonogestrel/Ethinyl Estradiol Vaginal Ring</td>
<td>ATV/r</td>
<td>Ethinyl estradiol AUC ↓ 26%</td>
<td>Use standard dose.</td>
</tr>
<tr>
<td>All other PIs</td>
<td>Etonogestrel AUC ↑ 79%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal Ethinyl Estradiol/Norelgestromin</td>
<td>LPV/r</td>
<td>↔ LPV</td>
<td>Use standard dose.</td>
</tr>
<tr>
<td>All other PIs</td>
<td>Ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%</td>
<td>Consider alternative or additional contraceptive method or alternative ARV drug.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs

_Last updated October 25, 2018; last reviewed October 25, 2018_ (page 14 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal Therapies, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal Hormone Replacement Therapy (HRT)</td>
<td>All PIs</td>
<td>↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)</td>
<td>Adjust estrogen dosage as needed based on clinical effects.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions</td>
<td>Adjust progestin/progesterone dosage as needed based on clinical effects. Because drospirenone is prescribed as a lower dose for menopausal HRT than the products used for hormonal contraceptives, it is not contraindicated with ATV/c products.</td>
</tr>
<tr>
<td>Gender-Affirming Hormone Therapy</td>
<td>All PIs</td>
<td>↓ estradiol possible</td>
<td>Adjust estradiol dosage as needed based on clinical effects and endogenous hormone concentrations.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>↔ finasteride, goserelin, leuprolide acetate, and spironolactone expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>↑ dutasteride possible</td>
<td>Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.</td>
</tr>
<tr>
<td></td>
<td>All PIs</td>
<td>↓ testosterone possible</td>
<td>Adjust testosterone dosage as needed based on clinical effects and endogenous hormone concentrations.</td>
</tr>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (unboosted), ATV/r</td>
<td>All PIs</td>
<td>↑ atorvastatin possible</td>
<td>Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities.</td>
</tr>
<tr>
<td>ATV/c</td>
<td>Atorvastatin AUC ↑ 9.2-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 18.9-fold</td>
<td>Coadministration is not recommended.</td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone</td>
<td>Titrate atorvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.</td>
<td></td>
</tr>
<tr>
<td>DRV/c</td>
<td>Atorvastatin AUC ↑ 3.9-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 4.2-fold</td>
<td>Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>Atorvastatin AUC ↑ 5.9-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 4.7-fold</td>
<td>Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.</td>
<td></td>
</tr>
<tr>
<td>TPV/r</td>
<td>Atorvastatin AUC ↑ 9.4-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 8.6-fold</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>All PIs</td>
<td>Significant ↑ lovastatin expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>All PIs</td>
<td>ATV ↑ pitavastatin AUC 31% and C&lt;sub&gt;max&lt;/sub&gt; ↑ 60% ↔ ATV</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LPV/r ↓ pitavastatin AUC 20% ↔ LPV</td>
<td></td>
</tr>
</tbody>
</table>
Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 15 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
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<th>Effect on PI and/ or Concomitant Drug Concentrations</th>
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</thead>
<tbody>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>ATV/c, ATP/r</td>
<td>No data</td>
<td>Titrate pravastatin dose carefully while monitoring for toxicities.</td>
</tr>
<tr>
<td></td>
<td>DRV/c, DRV/r</td>
<td>With DRV/r:</td>
<td>Titrate pravastatin dose carefully while monitoring for toxicities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pravastatin AUC ↑ 81% following single dose of pravastatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pravastatin AUC ↑ 23% at steady state</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Pravastatin AUC ↑ 33%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>ATV/r</td>
<td>Rosuvastatin AUC ↑ 3-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 7-fold</td>
<td>Titrate rosuvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 10 mg daily.</td>
</tr>
<tr>
<td></td>
<td>ATV/c</td>
<td>Rosuvastatin AUC ↑ 3.4-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 10.6-fold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/c</td>
<td>Rosuvastatin AUC ↑ 1.9-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 3.8-fold</td>
<td>Titrate rosuvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 20 mg daily.</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>Rosuvastatin AUC ↑ 48%, C&lt;sub&gt;max&lt;/sub&gt; ↑ 2.4-fold</td>
<td>Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Rosuvastatin AUC ↑ 2.1-fold, C&lt;sub&gt;max&lt;/sub&gt; ↑ 4.7-fold</td>
<td>Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed rosuvastatin 10 mg daily.</td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>Rosuvastatin AUC ↑ 26%, C&lt;sub&gt;max&lt;/sub&gt; ↑ 2.2-fold</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>All PIs</td>
<td>Significant ↑ simvastatin expected</td>
<td><strong>Contraindicated.</strong></td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, Everolimus, Sirolimus, Tacrolimus</td>
<td>All PIs</td>
<td>↑ immunosuppressant expected</td>
<td>Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.</td>
</tr>
</tbody>
</table>
## Concomitant Drug and Treatment for Opioid Dependence

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine Sublingual, buccal, or implant</td>
<td>ATV (unboosted)</td>
<td>Buprenorphine AUC ↑ 93% Norbuprenorphine(d) AUC ↑ 76% ↓ ATV possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>ATV/r</td>
<td>Buprenorphine AUC ↑ 66% Norbuprenorphine(d) AUC ↑ 105%</td>
<td>Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>No significant effect on buprenorphine Norbuprenorphine(d) AUC ↑ 46% and C(\text{min}) ↑ 71%</td>
<td>No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPV/r</td>
<td>No significant effect on buprenorphine Norbuprenorphine(d) AUC, C(\text{max}), and C(\text{min}) ↓ 80% TPV C(\text{Cmin}) ↓ 19% to 40%</td>
<td>Consider monitoring TPV level. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>Effects unknown</td>
<td>Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Clinical monitoring is recommended.</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>All PIs</td>
<td>↑ fentanyl possible</td>
<td>Clinical monitoring is recommended, including for potentially fatal respiratory depression.</td>
</tr>
<tr>
<td>Methadone</td>
<td>ATV (unboosted)</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td>Effects unknown</td>
<td>Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.</td>
</tr>
<tr>
<td></td>
<td>All PI/r</td>
<td>ATV/r and DRV/r ↓ R-methadone(e) AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% TPV/r ↓ R-methadone(e) AUC 48%</td>
<td>Opioid withdrawal is unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>All PIs</td>
<td>Oxycodone AUC ↑ 2.6-fold with LPV/r</td>
<td>Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>All PIs</td>
<td>↑ tramadol possible</td>
<td>Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.</td>
</tr>
</tbody>
</table>
### Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs  
_Last updated October 25, 2018; last reviewed October 25, 2018_  
(page 17 of 19)

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDE5 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avanafil</td>
<td>All PIs except unboosted ATV</td>
<td>RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold and ↑ C&lt;sub&gt;max&lt;/sub&gt; 2.4-fold</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td></td>
<td>ATV (unboosted)</td>
<td>No data</td>
<td>Avanafil dose should not exceed 50 mg once every 24 hours.</td>
</tr>
</tbody>
</table>
| **Sildenafil** | All PIs | DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone RTV 500 mg BID ↑ sildenafil AUC 1,000% | For Treatment of Erectile Dysfunction:  
  • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.  
For Treatment of PAH:  
  • Contraindicated. |
| **Tadalafil** | All PIs | RTV 200 mg BID ↑ tadalafil AUC 124%  
TPV/r (1st dose) ↑ tadalafil AUC 133%  
No significant effect on TPV/r steady state | For Treatment of Erectile Dysfunction:  
  • Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil.  
For Treatment of PAH  
  In Patients on a PI >7 Days:  
  • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.  
  In Patients on Tadalafil who Require a PI:  
  • Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.  
  In Patients Switching between COBI and RTV:  
  • Maintain tadalafil dose.  
  For Treatment of Benign Prostatic Hyperplasia:  
  • Maximum recommended daily dose is tadalafil 2.5 mg per day. |
| **Vardenafil** | All PIs | RTV 600 mg BID ↑ vardenafil AUC 49-fold | Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil. |
| **Sedative/Hypnotics** | | | |
| Alprazolam, Clonazepam, Diazepam | All PIs | ↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and ↑ AUC 248% | Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam. |
| Lorazepam, Oxazepam, Temazepam | All PIs | No data | These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines. |
| Midazolam | All PIs | ↑ midazolam expected | Oral midazolam is contraindicated with PIs.  
Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation. |
<p>| Suvorexant | All PIs | ↑ suvorexant expected | Coadministration is not recommended. |</p>
<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedative/Hypnotics, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Triazolam | All PIs | ↑ triazolam expected  
RTV (200 mg BID) ↑ triazolam half-life 1,200% and AUC 2,000% | Contraindicated. |
| Zolpidem | PI/c, PI/r | ↑ zolpidem possible | Initiate zolpidem at a low dose. Dose reduction may be necessary. |
| **Miscellaneous Drugs** |
| Calcifediol | All PIs | ↑ calcifediol possible | Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum calcium concentrations should be closely monitored. |
| Cisapride | All PIs | ↑ cisapride expected | Contraindicated. |
| Colchicine | All PIs | RTV 100 mg BID ↑ colchicine AUC 296% and C_max 184%  
Significant ↑ colchicine expected with all PIs, with or without COBI or RTV | For Treatment of Gout Flares:  
• Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.  
For Prophylaxis of Gout Flares:  
• Administer colchicine 0.3 mg once daily or every other day.  
For Treatment of Familial Mediterranean Fever:  
• Do not exceed colchicine 0.6 mg once daily or colchicine 0.3 mg BID.  
Do not coadminister in patients with hepatic or renal impairment. |
| Dronabinol | All PIs | ↑ dronabinol possible | Monitor for increased dronabinol-related adverse reactions. |
| Eluxadoline | All PIs | ↑ eluxadoline expected | Administer eluxadoline at a dose of 75 mg twice daily and monitor for eluxadoline-related adverse effects. |
| Enzalutamide | All PIs | ↓ PI expected | Contraindicated. |
| Ergot Derivatives | All PIs | ↑ dihydroergotamine, ergotamine, methylergonovine expected | Contraindicated. |
| Flibanserin | All PIs | ↑ fibanserin expected | Contraindicated. |
| Irinotecan | ATV (unboosted), ATV/c, ATV/r | ↑ irinotecan expected | Contraindicated. |
| Mitotane | All PIs | ↓ PI expected | Contraindicated. |
| Salmeterol | All PIs | ↑ salmeterol possible | Do not coadminister because of potential increased risk of salmeterol-associated CV events. |
### Key to Symbols:
- **↑** = increase
- **↓** = decrease
- **↔** = no change

### Key to Acronyms:
- 17-BMP = beclomethasone 17-monopropionate
- ALT = alanine aminotransferase
- ART = antiretroviral therapy
- ARV = antiretroviral
- ATV = atazanavir
- ATV/c = atazanavir/cobicistat
- ATV/r = atazanavir/ritonavir
- AUC = area under the curve
- BID = twice daily
- C<sub>max</sub> = maximum plasma concentration
- C<sub>min</sub> = minimum plasma concentration
- CNS = central nervous system
- COBI = cobicistat
- CrCl = creatinine clearance
- CV = cardiovascular
- CYP = cytochrome P
- DHA = dihydroartemisinin
- DRV = darunavir
- DRV/c = darunavir/cobicistat
- DRV/r = darunavir/ritonavir
- ECG = electrocardiogram
- eGFR = estimated glomerular filtration rate
- FPV = fosamprenavir
- HCV = hepatitis C virus
- HRT = hormone replacement therapy
- IDV = indinavir
- INR = international normalized ratio
- LPV = lopinavir
- LPV/r = lopinavir/ritonavir
- MPA = medroxyprogesterone acetate
- NFV = nelfinavir
- OATP = organic anion-transporting polypeptide
- PAH = pulmonary arterial hypertension
- PDE5 = Phosphodiesterase Type 5
- PI = protease inhibitor
- PI/c = protease inhibitor/cobicistat
- PI/r = protease inhibitor/ritonavir
- PK = pharmacokinetic
- PPI = proton pump inhibitor
- PTH = parathyroid hormone
- QTc = QT corrected for heart rate
- RTV = ritonavir
- SQV = saquinavir
- TDF = tenofovir disoproxil fumarate
- TPV = tipranavir
- TPV/r = tipranavir/ritonavir

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#### Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs

*Last updated October 25, 2018; last reviewed October 25, 2018*

- DHA is an active metabolite of artemether.
- The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulations may also be available): Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo.
- The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulations may also be available): Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl.
- Norbuprenorphine is an active metabolite of buprenorphine.
- R-methadone is the active form of methadone.
Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 1 of 10)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a, and 20b. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

**Note:** DLV is not included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions. The term “All NNRTIs” in this table refers to all NNRTIs except for DLV.

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>NNRTIa</th>
<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Reducers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>RPV</td>
<td>↓ RPV expected when given simultaneously</td>
<td>Give antacids at least 2 hours before or at least 4 hours after RPV.</td>
</tr>
<tr>
<td>H2 Receptor Antagonists</td>
<td>RPV</td>
<td>↓ RPV</td>
<td>Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.</td>
</tr>
<tr>
<td>PPIs</td>
<td>RPV</td>
<td>With Omeprazole 20 mg Daily:</td>
<td>Contraindicated. Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RPV AUC ↓ 40% and C_{min} ↓ 33%</td>
<td></td>
</tr>
<tr>
<td>Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfuzosin, Doxazosin, Silodosin</td>
<td>EFV, ETR, NVP</td>
<td>↓ alpha antagonist expected</td>
<td>Consider alternative therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>EFV, ETR, NVP</td>
<td>↓ tamsulosin expected</td>
<td>Monitor for therapeutic effectiveness of tamsulosin after 2 to 4 weeks of dosing. May need to increase to tamsulosin 0.8 mg once daily for patients who fail to respond to the 0.4 mg dose.</td>
</tr>
<tr>
<td>Anticoagulants/Antiplatelets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>EFV, ETR, NVP</td>
<td>↓ apixaban possible</td>
<td>Consider alternative therapy.</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>All NNRTIs</td>
<td>↔ betrixaban expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>EFV, ETR</td>
<td>↓ activation of clopidogrel possible</td>
<td>ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.</td>
</tr>
<tr>
<td></td>
<td>DOR, NVP, RPV</td>
<td>↔ clopidogrel expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>All NNRTIs</td>
<td>↔ dabigatran expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>All NNRTIs</td>
<td>↔ edoxaban expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>All NNRTIs</td>
<td>↔ prasugrel expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EFV, ETR, NVP</td>
<td>↓ rivaroxaban possible</td>
<td>Consider alternative therapy.</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>EFV, ETR, NVP</td>
<td>↓ ticagrelor expected</td>
<td>Consider alternative therapy.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>EFV, ETR, NVP</td>
<td>↑ or ↓ warfarin possible</td>
<td>Monitor INR and adjust warfarin dose accordingly.</td>
</tr>
<tr>
<td>Concomitant Drug Class/ Name</td>
<td>NNRTIa</td>
<td>Effect on NNRTI and/or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, Phenobarbital, Phenytoin</td>
<td></td>
<td>Concomitant Drug Class/ Name</td>
<td>Effect on NNRTI and/or Concomitant Drug Concentrations</td>
</tr>
</tbody>
</table>
| EFV | Carbamazepine plus EFV:  
• Carbamazepine AUC ↓ 27%  
• EFV AUC ↓ 36%  
Phenytoin plus EFV:  
• ↓ EFV  
• ↓ phenytoin possible | Monitor anticonvulsant and EFV concentrations or, if possible, use alternative anticonvulsant to those listed. |
| ETR | ↓ anticonvulsant and ETR possible | Do not coadminister. Consider alternative anticonvulsant. |
| NVP | ↓ anticonvulsant and NVP possible | Monitor anticonvulsant and NVP concentrations and virologic responses or consider alternative anticonvulsant. |
| DOR, RPV | ↓ NNRTI possible | Contraindicated. Do not coadminister. Consider alternative anticonvulsant. |
| Eslicarbazepine | All NNRTIs | ↓ NNRTI possible | Monitor virologic outcomes and consider monitoring plasma concentrations of ARVs, or consider alternative anticonvulsant or ARV drug. |
| Oxcarbazepine | DOR, RPV | ↓ NNRTI possible | Contraindicated. Do not coadminister. Consider alternative anticonvulsant. |
| Ethosuximide, Lacosamide, Tiagabine, Zonisamide | ETR, EFV | ↓ anticonvulsant possible | Monitor seizure control and plasma concentrations of anticonvulsants (when available). |
| Lamotrigine | EFV | ↓ lamotrigine possible | Monitor seizure control and plasma concentrations of lamotrigine. |
| Antidepressants             |        |                                                      |                                               |
| Bupropion | EFV, NVP | Bupropion AUC ↓ 55%  
↓ bupropion possible | Titrate bupropion dose based on clinical response. |
| Citalopram, Escitalopram | EFV, ETR, NVP | ↓ antidepressant possible | Titrate antidepressant dose based on clinical response. |
| Fluoxetine, Fluvoxamine | All NNRTIs | ↔ antidepressant expected | No dose adjustment necessary. |
| Paroxetine | EFV, ETR | ↔ paroxetine observed with EFV or ETR  
↔ expected with DOR, NVP or RPV | No dose adjustment necessary. |
| Nefazodone | EFV, ETR, NVP | ↓ nefazodone expected  
↑ NNRTI possible  
↑ NNRTI possible | Monitor the antidepressant effect and titrate dose as necessary. Monitor for ARV-related adverse events. |
<p>| Sertraline | EFV | Sertraline AUC ↓ 39% | Titrate sertraline dose based on clinical response. |
| Trazodone | EFV, ETR, NVP | ↓ trazodone possible | Monitor the therapeutic effect of trazodone and titrate dose as necessary. |</p>
<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>NNRTI(^a)</th>
<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>EFV</td>
<td>↔ fluconazole or EFV</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>ETR AUC ↑ 86%</td>
<td>No dose adjustment necessary. Use with caution.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>NVP AUC ↑ 110%</td>
<td>Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↑ NNRTI possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>EFV, ETR, NVP</td>
<td>↓ isavuconazole possible</td>
<td>Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole concentration and antifungal response.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↑ NNRTI possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>EFV</td>
<td>Itraconazole and OH-itraconazole AUC, (C_{\text{max}}), and (C_{\text{min}}) ↓ 35% to 44%</td>
<td>Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>↓ itraconazole possible</td>
<td>Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Itraconazole AUC ↓ 61%</td>
<td>Avoid this combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↑ NNRTI possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>EFV</td>
<td>Posaconazole AUC ↓ 50%</td>
<td>Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ EFV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DOR, ETR, NVP, RPV</td>
<td>↑ NNRTI possible</td>
<td>Monitor for NNRTI toxicities.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>EFV</td>
<td>Voriconazole AUC ↓ 77%</td>
<td>Contraindicated at standard doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFV AUC ↑ 44%</td>
<td>Dose Adjustment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Voriconazole 400 mg BID, EFV 300 mg daily</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>↔ Voriconazole AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ETR AUC ↑ 36%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>↓ voriconazole possible</td>
<td>Monitor for toxicity and antifungal response and/or voriconazole concentration.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↑ NNRTI possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Antihyperglycemics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin</td>
<td>All NNRTIs</td>
<td>↔ antihyperglycemic expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Linagliptin, Saxagliptin</td>
<td>EFV, ETR, NVP</td>
<td>↓ antihyperglycemic possible</td>
<td>Monitor glycemic control.</td>
</tr>
<tr>
<td>Concomitant Drug Class/ Name</td>
<td>NNRTI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Effect on NNRTI and/or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
</tbody>
</table>
| Artemether/ Lumefantrine     | EFV               | Artemether AUC ↓ 79%  
DHA AUC ↓ 75%  
Lumefantrine AUC ↑ 56% | Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy. |
|                             | ETR               | Artemether AUC ↓ 38%  
↔ DHA AUC  
↔ Lumefantrine AUC  
↔ ETR AUC | Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor for antimalarial efficacy. |
|                             | NVP               | Artemether AUC ↓ 67% to 72%  
DHA:  
• Study results are conflicting. DHA AUC ↓ 37% in one study, no difference in another.  
Lumefantrine:  
• Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another. | Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity. |
| Atovaquone/ Proguanil        | EFV               | Atovaquone AUC ↓ 75%  
Proguanil AUC ↓ 43% | No dose recommendation. Consider alternative drug for malaria prophylaxis, if possible. |
| Antimycobacterials           |                   |                                                  |                                             |
| Bedaquiline                  | EFV, ETR          | ↓ bedaquiline possible  
↔ bedaquiline AUC | Do not coadminister. |
|                             | NVP               | ↔ bedaquiline AUC | No dose adjustment necessary. |
| Clarithromycin               | EFV               | Clarithromycin AUC ↓ 39% | Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
|                             | ETR               | Clarithromycin AUC ↓ 39%  
ETR AUC ↑ 42% | Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
|                             | NVP               | Clarithromycin AUC ↓ 31%  
NVP AUC ↑ 26% | Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
|                             | RPV               | ↔ clarithromycin expected  
↑ RPV possible | Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment. |
| Rifabutin                    | DOR               | DOR AUC ↓ 50% | Increase DOR dose to 100 mg twice daily. No dose adjustment for rifabutin. |
|                             | EFV               | Rifabutin ↓ 38% | Dose:  
• Rifabutin 450–600 mg/day; or  
• Rifabutin 600 mg 3 times/week if EFV is not coadministered with a PI. |
|                             | ETR               | ↔ Rifabutin and metabolite AUC  
ETR AUC ↓ 37% | Do not coadminister ETR plus PI/r with rifabutin.  
Use rifabutin 300 mg once daily if ETR is administered without PI/r |
<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>NNRTI(^a)</th>
<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimycobacterials, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin, continued</td>
<td>NVP</td>
<td>Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24%</td>
<td>No dose adjustment necessary. Use with caution.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NVP C(_{\text{min}}) ↓ 16%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>Rifabutin plus RPV 50 mg Once Daily Compared to RPV 25 mg Once Daily Alone: • ↔ RPV AUC and C(_{\text{min}}) Increase RPV dose to 50 mg once daily. No dose adjustment for rifabutin.</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>DOR</td>
<td>DOR AUC ↓ 88%</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>EFV AUC ↓ 26%</td>
<td>Do not use EFV 400 mg with rifampin. Maintain EFV dose at 600 mg once daily and monitor for virologic response.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>Significant ↓ ETR possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>NVP ↓ 20% to 58%</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>RPV AUC ↓ 80%</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>EFV</td>
<td>↔ EFV concentrations</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ETR, NVP</td>
<td>↓ NNRTI possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↓ NNRTI expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td><strong>Antipneumocystis and Antitoxoplasmosis Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>EFV</td>
<td>Atovaquone AUC ↓ 44% to 47%</td>
<td>Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug. If used in combination, monitor therapeutic efficacy of atovaquone.</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>EFV, ETR, NVP</td>
<td>↓ aripiprazole expected</td>
<td>Monitor effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dosing recommendations.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>EFV, ETR, NVP</td>
<td>↓ brexpiprazole expected</td>
<td>Monitor effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>EFV, ETR, NVP</td>
<td>↓ cariprazine and ↑ or ↓ active metabolite possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>EFV</td>
<td>↓ olanzapine possible</td>
<td>Monitor effect of olanzapine.</td>
</tr>
<tr>
<td></td>
<td>DOR, ETR, NVP, RPV</td>
<td>↔ olanzapine expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Pimozide</td>
<td>EFV, ETR, NVP</td>
<td>↓ pimozide possible</td>
<td>Monitor therapeutic effectiveness of pimozide</td>
</tr>
<tr>
<td>Lurasidone, Pimavanserin, Quetiapine, Thioridazine</td>
<td>EFV, ETR, NVP</td>
<td>↓ antipsychotic possible</td>
<td>Monitor effect of antipsychotic.</td>
</tr>
</tbody>
</table>
Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 6 of 10)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>NNRTIa</th>
<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>EFV, ETR, NVP</td>
<td>↓ alprazolam possible</td>
<td>Monitor for therapeutic effectiveness of alprazolam.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>EFV, NVP</td>
<td>↓ diazepam possible</td>
<td>Monitor for therapeutic effectiveness of diazepam.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>↑ diazepam possible</td>
<td>Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>EFV</td>
<td>↔ lorazepam AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ETR, NVP</td>
<td>↔ lorazepam expected</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>EFV</td>
<td>↑ or ↓ midazolam possible</td>
<td>Monitor therapeutic effectiveness and toxicity of midazolam.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>Midazolam AUC ↓ 31%</td>
<td>Monitor therapeutic effectiveness of midazolam.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam active metabolite C&lt;sub&gt;max&lt;/sub&gt; ↑ 57%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>↓ midazolam possible</td>
<td>Monitor therapeutic effectiveness of midazolam.</td>
</tr>
<tr>
<td>Triazolam</td>
<td>EFV, ETR, NVP</td>
<td>↓ triazolam possible</td>
<td>Monitor therapeutic effectiveness of triazolam.</td>
</tr>
<tr>
<td><strong>Cardiac Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine CCBs</td>
<td>EFV, ETR, NVP</td>
<td>↓ CCBs possible</td>
<td>Titrate CCB dose based on clinical response.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem, Verapamil</td>
<td>EFV</td>
<td>Diltiazem AUC ↓ 69%</td>
<td>Titrate diltiazem or verapamil dose based on clinical response.</td>
</tr>
<tr>
<td></td>
<td>ETR, NVP</td>
<td>↓ diltiazem or verapamil possible</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>DOR, EFV, ETR, NVP</td>
<td>↓ NNRTI possible</td>
<td>Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>Significant ↓ RPV possible</td>
<td>Contraindicated with more than a single dose of dexamethasone.</td>
</tr>
<tr>
<td><strong>Hepatitis C Direct-Acting Antiviral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>EFV, ETR, NVP</td>
<td>Daclatasvir 120 mg Once Daily plus EFV 600 mg Daily Compared with Daclatasvir 60 mg Alone:  • Daclatasvir C&lt;sub&gt;min&lt;/sub&gt; ↓ 17%, AUC ↑ 37%</td>
<td>The recommended dose is daclatasvir 90 mg once daily.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>No data</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dasabuvir plus Paritaprevir/</td>
<td>DOR</td>
<td>↑ DOR possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ombitasivir/RTV</td>
<td>EFV</td>
<td>No data</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>ETR, NVP</td>
<td>↓ DAAs possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>RPV AUC ↓ 150% to 225%</td>
<td>Do not coadminister, due to potential for QT interval prolongation with higher concentrations of RPV.</td>
</tr>
</tbody>
</table>
### Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 10)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>NNRTI(^a)</th>
<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C Direct-Acting Antiviral Agents, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Elbasvir/ Grazoprevir | EFV | Elbasvir AUC ↓ 54%  
Grazoprevir AUC ↓ 83%  
EFV ↔ by grazoprevir  
EFV ↔ AUC by elbasvir | | Contraindicated. |
| | ETR, NVP | ↓ elbasvir and grazoprevir expected | Do not coadminister. |
| | DOR, RPV | ↔ Elbasvir, grazoprevir  
↔ DOR, RPV | No dose adjustment necessary. |
| Gilevaprevir/ Pibrentasvir | DOR | ↑ DOR expected | No dose adjustment necessary. |
| | EFV | ↓ gilevaprevir and pibrentasvir expected | No dose adjustment necessary. |
| | ETR, NVP | ↓ gilevaprevir and pibrentasvir possible | No dose adjustment necessary. |
| | RPV | ↔ gilevaprevir, pibrentasvir  
RPV AUC ↑ 84% | |
| Ledipasvir/ Sofosbuvir | EFV | Ledipasvir AUC, C\(_{\text{min}}\text{, and } C_{\text{max}}\) ↓ 34%  
↔ sofosbuvir | No dose adjustment necessary. |
| | ETR, NVP | No significant effect expected | |
| | DOR, RPV | ↔ Ledipasvir, sofosbuvir  
↔ DOR, RPV | |
| Simeprevir | DOR | No significant effect expected | No dose adjustment necessary. |
| | EFV | Simeprevir AUC ↓ 71%, C\(_{\text{min}}\) ↓ 91%  
↔ EFV | Do not coadminister. |
| | ETR, NVP | ↓ simeprevir expected | Do not coadminister. |
| | RPV | ↔ simeprevir and RPV | No dose adjustment necessary. |
| Sofosbuvir/ Velpatasvir | EFV | Velpatasvir AUC ↓ 43%, C\(_{\text{max}}\) ↓ 37% and C\(_{\text{min}}\) ↓ 47%  
↔ velpatasvir | Do not coadminister. |
| | ETR, NVP | ↓ velpatasvir expected | Do not coadminister. |
| | DOR, RPV | No significant effect expected | No dose adjustment necessary. |
| Sofosbuvir/ Velpatasvir/ Voxilaprevir | EFV | Velpatasvir AUC ↓ 43%, C\(_{\text{max}}\) ↓ 37%, and C\(_{\text{min}}\) ↓ 47%  
↓ voxilaprevir expected  
↓ velpatasvir expected | Do not coadminister. |
| | ETR, NVP | ↓ voxilaprevir expected  
↓ velpatasvir expected | Do not coadminister. |
| | DOR, RPV | No significant effect expected | No dose adjustment necessary. |
### Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs *(Last updated October 25, 2018; last reviewed October 25, 2018)* *(page 8 of 10)*

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
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<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herbal Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>EFV, ETR, NVP</td>
<td>↓ EFV, ETR, and NVP expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↓ NNRTI expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td><strong>Hormonal Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal Contraceptives, Oral</strong></td>
<td>EFV</td>
<td>↔ Ethinyl estradiol</td>
<td>Use alternative or additional contraceptive methods.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etonogestrel (metabolite of oral desogestrel) C&lt;sub&gt;min&lt;/sub&gt; ↓ 61%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levonorgestrel (metabolite of oral norgestimate) AUC ↓ 83%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norelgestromin (metabolite of oral norgestimate) AUC ↓ 64%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>Ethinyl estradiol AUC ↑ 22%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant effect on norethindrone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Ethinyl estradiol AUC ↓ 29%, C&lt;sub&gt;min&lt;/sub&gt; ↓ 58%</td>
<td>Based on clinical data demonstrating no change in effectiveness, no dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norethindrone AUC ↓ 18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etonogestrel (metabolite of oral desogestrel) C&lt;sub&gt;min&lt;/sub&gt; ↓ 22%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>↔ Ethinyl estradiol</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ Norethindrone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DOR</td>
<td>↔ Ethinyl estradiol</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ Levonorgestrel</td>
<td></td>
</tr>
<tr>
<td><strong>Depot Medroxyprogesterone Acetate (MPA) Injectable</strong></td>
<td>EFV, NVP</td>
<td>DMPA: no significant change</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Etonogestrel-Releasing Subdermal Implant</strong></td>
<td>EFV</td>
<td>Etonogestrel AUC ↓ 63% to 82%</td>
<td>Use alternative or additional contraceptive methods.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Etonogestrel: no significant change</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Etonogestrel/Ethinyl Estradiol Vaginal Ring</strong></td>
<td>EFV</td>
<td>Ethinyl estradiol (intravaginal ring) AUC ↓ 56%</td>
<td>Use alternative or additional contraceptive methods.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etonogestrel (intravaginal ring) AUC ↓ 81%</td>
<td></td>
</tr>
<tr>
<td><strong>Levonorestrel-Releasing Subdermal Implant</strong></td>
<td>EFV</td>
<td>Levonorgestrel AUC ↓ 47%</td>
<td>Use alternative or additional contraceptive methods. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Levonorgestrel AUC ↑ 35%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Levonorgestrel For emergency contraception</strong></td>
<td>EFV</td>
<td>Levonorgestrel AUC ↓ 58%</td>
<td>Effectiveness of emergency postcoital contraception may be diminished.</td>
</tr>
</tbody>
</table>

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

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 10)

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<thead>
<tr>
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<th>Effect on NNRTI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Therapies, continued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal Hormone Replacement Therapy</td>
<td>EFV, ETR, NVP</td>
<td>↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic) ↓ medroxyprogesterone possible ↓ micronized progesterone possible ↓ drospirenone possible See Hormonal Contraceptives for other progestin-NNRTI interactions</td>
<td>Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.</td>
</tr>
<tr>
<td>Gender-Affirming Hormone Therapy</td>
<td>EFV, ETR, NVP</td>
<td>↓ estradiol possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible</td>
<td>Monitor feminizing effects of estrogen and antiandrogen therapy and titrate dosing as necessary to achieve therapeutic goals.</td>
</tr>
<tr>
<td></td>
<td>EFV, ETR, NVP</td>
<td>↓ testosterone possible</td>
<td>Monitor masculinizing effects of testosterone and titrate testosterone dose as necessary to achieve therapeutic goals.</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>EFV, ETR</td>
<td>Atorvastatin AUC ↓ 32% to 43%</td>
<td>Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>↓ atorvastatin possible</td>
<td>Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.</td>
</tr>
<tr>
<td></td>
<td>DOR, RPV</td>
<td>↔ atorvastatin AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>EFV, ETR</td>
<td>↑ fluvastatin possible</td>
<td>Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.</td>
</tr>
<tr>
<td>Lovastatin, Simvastatin</td>
<td>EFV</td>
<td>Simvastatin AUC ↓ 68% Simvastatin active metabolite AUC ↓ 60%</td>
<td>Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided.</td>
</tr>
<tr>
<td></td>
<td>ETR, NVP</td>
<td>↓ lovastatin possible ↓ simvastatin possible</td>
<td>Adjust lovastatin or simvastatin dose according to lipid responses but do not exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided.</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>EFV</td>
<td>↔ pitavastatin AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DOR, ETR, NVP, RPV</td>
<td>↔ pitavastatin expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>EFV</td>
<td>Pravastatin AUC ↓ 44%</td>
<td>Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>↓ pravastatin possible</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>EFV, ETR, NVP</td>
<td>↔ rosuvastatin expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Concomitant Drug Class/ Name</td>
<td>NNRTI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Effect on NNRTI and/or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclomorphine, Everolimus, Sirolimus, Tacrolimus</td>
<td>EFV, ETR, NVP</td>
<td>↓ immunosuppressant possible</td>
<td>Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.</td>
</tr>
<tr>
<td><strong>Narcotics/Treatments for Opioid Dependence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine Sublingual or buccal</td>
<td>EFV</td>
<td>Buprenorphine AUC ↓ 50%</td>
<td>No dose adjustment recommended; monitor for withdrawal symptoms.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>Buprenorphine AUC ↓ 25%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Buprenorphine Implant</td>
<td>EFV, ETR, NVP</td>
<td>No data</td>
<td>Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant.</td>
</tr>
<tr>
<td>Methadone</td>
<td>EFV</td>
<td>Methadone AUC ↓ 52%</td>
<td>Opioid withdrawal common; increased methadone dose often necessary.</td>
</tr>
<tr>
<td></td>
<td>DOR, ETR, NVP</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>PDE5 Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>DOR, RPV</td>
<td>↔ sildenafil expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ETR</td>
<td>Sildenafil AUC ↓ 57%</td>
<td>May need to titrate sildenafil dose based on clinical effect.</td>
</tr>
<tr>
<td></td>
<td>EFV, NVP</td>
<td>↓ sildenafil possible</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>EFV, ETR, NVP</td>
<td>↓ tadalafil possible</td>
<td>May need to titrate tadalafil dose based on clinical effect.</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>↔ tadalafil</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Avanafil, Vardenafil</td>
<td>EFV, ETR, NVP</td>
<td>↓ PDE5 inhibitor possible</td>
<td>May need to increase PDE5 inhibitor dose based on clinical effect.</td>
</tr>
<tr>
<td><strong>Miscellaneous Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>All NNRTIs</td>
<td>↓ NNRTI expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Mitotané</td>
<td>All NNRTIs</td>
<td>↓ NNRTI expected</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 mg to 150 mg per dose.

<sup>b</sup> Norbuprenorphine is an active metabolite of buprenorphine.

<sup>c</sup> R-methadone is the active form of methadone.

**Key to Symbols:**

↑ = increase  
↓ = decrease  
↔ = no change

**Key to Acronyms:**  
ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blocker; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; DAA = direct-acting antiviral; DHA = dihydroartemisinin; DMPA = depot medroxyprogesterone acetate; DOR = doravirine; EFV = efavirenz; ETR = etravirine; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = Mycobacterium avium complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = Pneumocystis jirovecii pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PIII = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir
Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) *(Last updated October 25, 2018; last reviewed October 25, 2018)*

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

**Note:** Interactions associated with ddI and d4T are **not** included in this table. Please refer to FDA product labels for information regarding interactions between ddI or d4T and other concomitant drugs.

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>NRTI</th>
<th>Effect on NRTI and/or Concomitant Drug Concentrations</th>
<th>Dosage Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytomegalovirus and Hepatitis B Antivirals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>TDF</td>
<td>No data</td>
<td>Do not coadminister. Serum concentrations of TDF and/or other renally eliminated drugs may increase.</td>
</tr>
<tr>
<td>Ganciclovir, Valganciclovir</td>
<td>TAF, TDF</td>
<td>No data</td>
<td>Serum concentrations of ganciclovir and/or TFV may increase. Monitor for dose-related toxicities.</td>
</tr>
<tr>
<td></td>
<td>ZDV</td>
<td>No significant effect</td>
<td>Potential increase in hematologic toxicities.</td>
</tr>
<tr>
<td><strong>Hepatitis C Antiviral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>TAF, TDF</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir, Sofosbuvir/Velpatasvir, Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>TAF, TDF</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>Ledipasvir ↑ TFV AUC 40% to 98% with TDF given with RPV and EFV. Further ↑ TFV possible if TDF is given with PIs.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No dose adjustment necessary.</td>
<td>The safety of increased TFV exposure when ledipasvir/sofosbuvir is coadministered with TDF plus a PI/r or PI/c has not been established. Consider alternative HCV or ARV drugs to avoid increased TFV toxicities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider using TAF in patients at risk of TDF-associated adverse events. If TDF is used in these patients, monitor for TDF toxicity.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coadministration of ledipasvir/sofosbuvir with EVGc/TDF/FTC is not recommended.</td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>TDF</td>
<td>With Sofosbuvir 400 mg: ↔ TFV AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ZDV</td>
<td>Ribavirin inhibits phosphorylation of ZDV.</td>
<td>Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.</td>
</tr>
<tr>
<td><strong>INSTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG</td>
<td>TAF</td>
<td>↔ TAF AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>↔ TDF AUC</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ DTG AUC</td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td>TDF</td>
<td>RAL AUC ↑ 49%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Narcotics/Treatment for Opioid Dependence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>3TC, TDF, TAF, ZDV</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
</tbody>
</table>
Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) *(Last updated October 25, 2018; last reviewed October 25, 2018)*

(page 2 of 3)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>NRTI</th>
<th>Effect on NRTI and/or Concomitant Drug Concentrations</th>
<th>Dosage Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narcotics/Treatment for Opioid Dependence, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>ABC</td>
<td>Methadone clearance ↑ 22%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>ZDV</td>
<td>ZDV AUC ↑ 29% to 43%</td>
<td>Monitor for ZDV-related adverse effects.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>ZDV</td>
<td>ZDV AUC ↑ 31%</td>
<td>Monitor for ZDV-related adverse effects.</td>
</tr>
</tbody>
</table>
| **Anticonvulsants** | TAF | With Carbamazepine:  
• TAF AUC ↓ 55%  
↓ TAF possible with other anticonvulsants | Coadministration is not recommended. |
| Carbamazepine, oxcarbazepine, phenobarbital, phenytoin | | | |
| **Antimycobacterial** | TAF | TAF AUC ↓ 55%  
TFV-DP (intracellular active moiety) AUC ↓ 36%  
TAF plus Rifampin Compared with TDF Alone:  
• TFV-DP (intracellular active moiety) AUC ↑ 4.2-fold  
With Twice-Daily TAF 25 mg Compared with Once-Daily TAF without Rifampin:  
• TAF AUC ↓ 14%  
• TFV-DP (intracellular active moiety) AUC ↓ 24% | Coadministration is not recommended. |
| Rifampin | TDF | ↔ AUC TFV | No dose adjustment necessary. |
| Rifabutin, Rifapentine | TAF | ↓ TAF possible | Coadministration is not recommended. |
| **St. John's Wort** | TAF | ↓ TAF possible | Coadministration is not recommended. |
| **PIs (HIV)** | | | |
| ATV (Unboosted), ATV/c, ATV/r | TAF | TAF 10 mg with ATV/r:  
• TAF AUC ↑ 91%  
TAF 10 mg with ATV/c:  
• TAF AUC ↑ 75%  
TDF With ATV (Unboosted):  
• ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV)  
TFV AUC ↑ 24% to 37% | No dose adjustment (use TAF 25 mg).  
Avoid concomitant use without RTV or COBI. |
| | TDF | With ATV (Unboosted):  
• ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV)  
TFV AUC ↑ 24% to 37% | Avoid concomitant use without RTV or COBI. Dose:  
• ATV 300 mg daily plus (RTV 100 mg or COBI 150 mg) daily when coadministered with TDF 300 mg daily  
• If using TDF and H2 receptor antagonist in an ART-experienced patient, use ATV 400 mg daily plus (RTV 100 mg or COBI 150 mg) daily  
Monitor for TDF-associated toxicity. |
| | ZDV | With ATV (Unboosted):  
• ZDV C_{min} ↓ 30% and ↔ ZDV AUC | Clinical significance unknown. |
## Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents)

*Last updated October 25, 2018; last reviewed October 25, 2018*

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>NRTI</th>
<th>Effect on NRTI and/or Concomitant Drug Concentrations</th>
<th>Dosage Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs (HIV), continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DRV/c</strong></td>
<td>TAF 25 mg with DRV/c:</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>↔ TAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>↑ TDF possible</td>
<td>Monitor for TDF-associated toxicity.</td>
<td></td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>TAF 10 mg with DRV/r:</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>↔ TAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>TFV AUC ↑ 22% and Cmin ↑ 37%</td>
<td>Clinical significance unknown. Monitor for TDF-associated toxicity.</td>
<td></td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td>TAF 10 mg with DRV/r:</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>↑ TAF AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>↔ LPV/r AUC</td>
<td>Clinical significance unknown. Monitor for TDF-associated toxicity.</td>
<td></td>
</tr>
<tr>
<td><strong>TPV/r</strong></td>
<td>ABC AUC ↓ 35% to 44%</td>
<td>Appropriate doses for this combination have not been established.</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>↓ TAF AUC</td>
<td>Coadministration is not recommended.</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>↔ TDF AUC</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td><strong>ZDV</strong></td>
<td>ZDV AUC ↓ 31% to 42%</td>
<td>Appropriate doses for this combination have not been established.</td>
<td></td>
</tr>
</tbody>
</table>

### Key to Symbols:

- ↑ = increase
- ↓ = decrease
- ↔ = no change

### Key to Acronyms:

- 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; Cmin = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitors; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 1 of 15)

This table provides information on known or predicted PK interactions between INSTIs (BIC, DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ alfuzosin expected</td>
<td>Contraindicated.</td>
<td></td>
</tr>
<tr>
<td>Doxazosin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ doxazosin possible</td>
<td>Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.</td>
<td></td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ tamsulosin expected</td>
<td>Coadministration is not recommended.</td>
<td></td>
</tr>
<tr>
<td>Terazosin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ terazosin possible</td>
<td>Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.</td>
<td></td>
</tr>
<tr>
<td>Silodosin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ silodosin expected</td>
<td>Contraindicated.</td>
<td></td>
</tr>
<tr>
<td><strong>Acid Reducers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI, Mg, +/- Ca-Containing Antacids</td>
<td>BIC</td>
<td>↔ BIC AUC if antacid is given 2 hours after BIC and under fasting conditions</td>
<td>With Antacids Containing Al/Mg or Ca:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BIC AUC ↓ 79% if given simultaneously with antacid</td>
<td>• BIC can be taken under fasting conditions at least 2 hours before antacids containing Al/Mg or Ca.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BIC AUC ↓ 52% if antacid is given 2 hours before BIC</td>
<td>Do not coadminister BIC simultaneously with, or 2 hours after, antacids containing Al/Mg or Ca.</td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td>DTG AUC ↓ 74% if given simultaneously with antacid</td>
<td>Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTG AUC ↓ 26% if given 2 hours before antacid</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>EVG AUC ↓ 40% to 50% if given simultaneously with antacid</td>
<td>Separate EVG/c/TDF/FTC and antacid administration by &gt;2 hours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EVG AUC ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval</td>
<td></td>
</tr>
</tbody>
</table>
### Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs  
(Last updated October 25, 2018; last reviewed October 25, 2018)  (page 2 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acid Reducers, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Al, Mg, +/- Ca-Containing Antacids, continued | RAL  | RAL/Mg Hydroxide Antacid:  
- RAL C<sub>min</sub> ↓ 49% to 63%  
- CaCO<sub>3</sub> Antacid:  
- RAL (400 mg BID) C<sub>min</sub> ↓ 32%  
- RAL (1200 mg once daily) C<sub>min</sub> ↓ 48% to 57% | Do not coadminister RAL and Al-Mg hydroxide antacids. Use alternative acid reducing agent.  
With CaCO<sub>3</sub> Antacids:  
- RAL 1200 mg once daily: **Do not coadminister.**  
- RAL 400 mg BID: No dose adjustment or separation necessary. |
| **H2-Receptor Antagonists** | BIC, DTG, EVG/c, RAL | No significant effect | No dose adjustment necessary. |
| **PPIs** | BIC, DTG, EVG/c, RAL | No significant effect | No dose adjustment necessary. |
| **Anticoagulants and Antiplatelets** |       |                                                   |                                           |
| Apixaban | BIC, DTG, RAL | ↔ expected | In Patients Requiring Apixaban 2.5 mg Twice Daily:  
- **Coadministration is not recommended.**  
In Patients Requiring Apixaban 5 mg or 10 mg Twice Daily:  
- Reduce apixaban dose by 50%. |
| Betrixaban | BIC, DTG, RAL | ↔ expected | Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily. |
| Dabigatran | BIC, DTG, RAL | ↔ expected | Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instruction when used with P-gp inhibitors. |
| Edoxaban | BIC, DTG, RAL | ↔ expected | For Stroke Prevention in Nonvalvular Atrial Fibrillation:  
- **No dose adjustment necessary.**  
For Deep Venous Thrombosis and Pulmonary Embolism:  
- Administer edoxaban 30 mg once daily. |
| Rivaroxaban | BIC, DTG, RAL | ↔ expected | No dose adjustment necessary.  
**Coadministration is not recommended.** |
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs *(Last updated October 25, 2018; last reviewed October 25, 2018)*

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
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<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulants and Antiplatelets, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ ticagrelor expected</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Vorapaxar</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ vorapaxar expected</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ or ↓ warfarin possible</td>
<td>Monitor INR and adjust warfarin dose accordingly.</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>BIC</td>
<td>↓ BIC possible</td>
<td>Consider using an alternative anticonvulsant or ARV.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>DTG AUC ↓ 49%</td>
<td>Increase DTG dose to 50 mg BID in treatment-naive or treatment-experienced, INSTI-naive patients. Use alternative anticonvulsant for INSTI-experienced patients with known or suspected INSTI resistance.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Carbamazepine AUC ↑ 43%</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>EVG AUC ↓ 69% and Cmin ↓ &gt;99%</td>
<td>↓ COBI expected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↓ or ↔ RAL possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>All INSTIs</td>
<td>↓ INSTI possible</td>
<td>Consider using an alternative anticonvulsant or ARV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ COBI possible</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ ethosuximide possible</td>
<td>Clinically monitor for ethosuximide toxicities.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>No data</td>
<td>Monitor anticonvulsant level and adjust dose accordingly.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>All INSTIs</td>
<td>↓ INSTI possible</td>
<td>Consider using an alternative anticonvulsant or ARV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ COBI possible</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>BIC</td>
<td>↓ BIC possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>↓ DTG possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↓ EVG/c expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↓ or ↔ RAL possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>BIC</td>
<td>↓ BIC possible</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>All INSTIs</td>
<td>No data</td>
<td>Monitor valproic acid concentration and virologic response.</td>
</tr>
<tr>
<td>Concomitant Drug Class/Name</td>
<td>INSTI</td>
<td>Effect on INSTI or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------</td>
<td>---------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Antidepressants/Anxiolytics/Antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Also see Sedative/Hypnotics section below.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ aripiprazole expected</td>
<td>Administer 25% of the usual aripiprazole dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Titrate based on clinical monitoring for efficacy and toxicity. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ brexpiprazole expected</td>
<td>Administer 25% of the usual brexpiprazole dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Titrate based on clinical monitoring for efficacy/toxicity. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ bupropion possible</td>
<td>Titrate bupropion dose based on clinical response.</td>
</tr>
<tr>
<td>Buspirone</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ buspirone possible</td>
<td>Initiate buspirone at a low dose. Dose reduction may be necessary.</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ cariprazine expected</td>
<td>Starting Cariprazine in a Patient Already on EVG/c:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• From Day 4 onward, administer 1.5 mg daily. Can be increased to a maximum dose of 3 mg daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If EVG/c is withdrawn, cariprazine dose may need to be increased.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Starting EVG/c in a Patient Already on Cariprazine:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If EVG/c is withdrawn, cariprazine dose may need to be increased.</td>
</tr>
</tbody>
</table>
### Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs

*Last updated October 25, 2018; last reviewed October 25, 2018*  
(page 5 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
</table>
| **Antidepressants/Anxiolytics/Antipsychotics, continued**  
Also see Sedative/Hypnotics section below. | | | |
| Fluvoxamine | **BIC, DTG, RAL** | ↔ expected | No dose adjustment necessary.  
↑ or ↓ EVG possible  
Consider alternative antidepressant or ARV. |
| Lurasidone | **BIC, DTG, RAL** | ↔ expected | No dose adjustment necessary.  
↑ lurasidone expected  
Contraindicated. |
| Pimavanserin | **BIC, DTG, RAL** | ↔ expected | Standard doses.  
EVG/c  
↑ pimavanserin expected  
Reduce pimavanserin dose by 50%. Titrate dose based on efficacy and toxicity. |
| Pimozide | **BIC, DTG, RAL** | ↔ expected | No dose adjustment necessary.  
↑ pimozide expected  
Contraindicated. |
| Quetiapine | **BIC, DTG, RAL** | ↔ expected | No dose adjustment necessary.  
↑ quetiapine AUC expected  
Initiation of Quetiapine in a Patient Receiving EVG/c:  
• Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects.  
Initiation of EVG/c in a Patient Receiving a Stable Dose of Quetiapine:  
• Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects. |
| **SSRIs**  
Citalopram, escitalopram, fluoxetine, paroxetine, sertraline | | | |
| | **EVG/c** | ↔ EVG  
↔ sertraline  
↑ other SSRI possible | No dose adjustment necessary. |
| | **BIC, DTG, RAL** | ↔ BIC, DTG, RAL expected  
↔ SSRI expected | |
| **TCAs**  
Amitriptyline, desipramine, doxepin, imipramine, nortriptyline | | | |
| | **EVG/c** | ↔ expected | No dose adjustment necessary.  
Desipramine AUC ↑ 65%  
↑ TCA expected  
Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels. |
| **Trazodone** | **BIC, DTG, RAL** | ↔ expected | No dose adjustment necessary.  
↑ trazodone possible  
Initiate with lowest dose of trazodone and titrate dose carefully. |
| **Other Antipsychotics**  
(CYP3A4 and/or CYP2D6 substrates) | **EVG/c** | ↑ antipsychotic possible | Initiate antipsychotic at a low dose. Decrease in antipsychotic dose may be necessary. |
# Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018)

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>BIC</td>
<td>↑ BIC possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ isavuconazole expected</td>
<td>If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ EVG and COBI possible</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>BIC</td>
<td>↑ BIC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ itraconazole expected</td>
<td>Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (&gt;200 mg/day) are not recommended unless dose is guided by itraconazole levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ EVG and COBI possible</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>BIC</td>
<td>↑ BIC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ EVG and COBI possible</td>
<td>If coadministered, monitor posaconazole concentrations.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>BIC</td>
<td>↑ BIC possible</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ voriconazole expected</td>
<td>Do not coadminister voriconazole and COBI unless benefit outweighs risk. If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ EVG and COBI possible</td>
<td></td>
</tr>
<tr>
<td><strong>Antihyperglycemics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>BIC</td>
<td>Metformin AUC ↑ 39%</td>
<td>Monitor for metformin adverse effects.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>DTG 50 mg Once Daily plus Metformin 500 mg BID:</td>
<td>Start metformin at lowest dose and titrate based on glycemic control. Monitor for metformin adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metformin AUC ↑ 79% and C&lt;sub&gt;max&lt;/sub&gt; ↑ 66%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTG 50 mg BID plus Metformin 500 mg BID:</td>
<td>When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse effects of metformin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metformin AUC ↑ 2.4-fold and C&lt;sub&gt;max&lt;/sub&gt; ↑ 2-fold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ saxagliptin expected</td>
<td>Limit saxagliptin dose to 2.5 mg once daily.</td>
</tr>
<tr>
<td>Dapagliflozin/ Saxagliptin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ saxagliptin expected</td>
<td>Do not coadminister, as this coformulated drug contains 5 mg of saxagliptin.</td>
</tr>
<tr>
<td><strong>Antimycobacterials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ clarithromycin possible</td>
<td>CrCl 50–60 mL/min:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ COBI possible</td>
<td>• Reduce clarithromycin dose by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CrCl &lt;50 mL/min:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• EVG/c is not recommended.</td>
</tr>
</tbody>
</table>
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018)  

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
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<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimycobacterials, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>BIC</td>
<td>Rifabutin (300 mg Once Daily):&lt;br&gt;• BIC AUC ↓ 38% and Cmin ↓ 56%</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>Rifabutin (300 mg Once Daily):&lt;br&gt;• DTG AUC ↔ and Cmin ↓ 30%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Rifabutin 150 mg Every Other Day with EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone:&lt;br&gt;• ↔ rifabutin AUC&lt;br&gt;• 25-O-desacetyl-rifabutin AUC ↑ 625%&lt;br&gt;• EVG AUC ↓ 21% and Cmin ↓ 67%</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>RAL AUC ↑ 19% and Cmin ↓ 20%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>BIC</td>
<td>BIC AUC ↓ 75%</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>Rifampin with DTG 50 mg BID Compared to DTG 50 mg BID Alone:&lt;br&gt;• DTG AUC ↓ 54% and Cmin ↓ 72%&lt;br&gt;Rifampin with DTG 50 mg BID Compared to DTG 50 mg Once Daily Alone:&lt;br&gt;• DTG AUC ↑ 33% and Cmin ↑ 22%</td>
<td>Dose:&lt;br&gt;• DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation.&lt;br&gt;Alternative to rifampin should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using rifabutin.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Significant ↓ EVG and COBI expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>RAL 400 mg:&lt;br&gt;• RAL AUC ↓ 40% and Cmin ↓ 61%&lt;br&gt;Rifampin with RAL 800 mg BID Compared to RAL 400 mg BID Alone:&lt;br&gt;• RAL AUC ↑ 27% and Cmin ↓ 53%</td>
<td>Dose:&lt;br&gt;• RAL 800 mg BID, instead of 400 mg BID&lt;br&gt;Do not coadminister RAL 1200 mg once daily with rifampin.&lt;br&gt;Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>BIC, DTG, EVG/c</td>
<td>Significant ↓ BIC, DTG, EVG, and COBI expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>Rifapentine 900 mg Once Weekly:&lt;br&gt;• RAL AUC ↑ 71% and Cmin ↓ 12%&lt;br&gt;Rifapentine 600 mg Once Daily:&lt;br&gt;• RAL Cmin ↓ 41%</td>
<td>For once-weekly rifapentine, use standard RAL 400 mg BID doses. Do not coadminister with once-daily rifapentine.</td>
</tr>
</tbody>
</table>
### Concomitant Drug Class/Name

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>BIC, DTG</td>
<td>↔ expected for the listed antiarrhythmics, except for disopyramide</td>
<td>No dose adjustment necessary. Coadminister with caution. Clinical monitoring is recommended.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ expected for the listed antiarrhythmics</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ antiarrhythmics possible</td>
<td>Use antiarrhythmics with caution. TDM, if available, is recommended for antiarrhythmics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digoxin C_max ↑ 41% and no significant change in AUC</td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>BIC, DTG</td>
<td>↑ BIC, DTG possible</td>
<td>Standard doses: No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ expected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ bosentan possible</td>
<td>In Patients on EVG/c ≥10 Days:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Start bosentan at 62.5 mg once daily or every other day based on individual tolerability.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In Patients on Bosentan Who Require EVG/c:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.</td>
</tr>
<tr>
<td>Beta-blockers (e.g., metoprolol, timolol)</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary. Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ beta-blockers possible</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>BIC</td>
<td>↑ BIC possible with diltiazem</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DTG, RAL</td>
<td>↔ expected for all other CCBs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ CCBs possible</td>
<td>Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 19a for diltiazem plus ATV/r recommendations.</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>BIC, DTG</td>
<td>↑ dofetilide expected</td>
<td>Contraindicated. No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ dofetilide possible</td>
<td>Do not coadminister. Contraindicated.</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ eplerenone expected</td>
<td>Contraindicated. No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ ranolazine expected</td>
<td>Contraindicated. No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>Contraindicated. No dose adjustment necessary.</td>
</tr>
</tbody>
</table>
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>BIC, DTG, EVG/c, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Inhaled or intranasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide, Budesonide</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ciclesonide, Fluticasone,</td>
<td></td>
<td>↑ glucocorticoid possible</td>
<td>Coadministration can result in adrenal insufficiency and Cushing’s syndrome. Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects. Consider an alternative corticosteroid (e.g., beclomethasone).</td>
</tr>
<tr>
<td>Mometasone</td>
<td></td>
<td>↓ EVG possible</td>
<td>Coadministration can result in adrenal insufficiency and Cushing’s syndrome. Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.</td>
</tr>
<tr>
<td>Inhaled or intranasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Systemic, Local injections, including intra-articular, epidural, or intra-orbital</td>
<td></td>
<td>↑ glucocorticoids expected</td>
<td>Do not coadminister. Coadministration may result in adrenal insufficiency and Cushing’s syndrome.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>BIC</td>
<td>↓ BIC possible</td>
<td>Consider an alternative corticosteroid for long-term use or an alternative ARV. If coadministration is necessary, monitor virologic response to ART.</td>
</tr>
<tr>
<td>Systemic</td>
<td>DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ EVG and COBI possible</td>
<td>Consider an alternative corticosteroid for long-term use or alternative ART. If coadministration is necessary, monitor virologic response to ART.</td>
</tr>
<tr>
<td>Prednisone, Prednisolone</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td>↑ prednisolone possible</td>
<td>Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministered, monitor for adrenal insufficiency and Cushing’s syndrome.</td>
</tr>
<tr>
<td>Hepatitis C Direct Acting Antivirals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>DTG</td>
<td>↔ daclatasvir</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ daclatasvir</td>
<td>Decrease daclatasvir dose to 30 mg once daily.</td>
</tr>
<tr>
<td></td>
<td>BIC, RAL</td>
<td>No data</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dasabuvir plus Ombitasvir/Paritaprevir/RTV</td>
<td>BIC, DTG</td>
<td>No data</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>No data</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>RAL AUC ↑ 134%</td>
<td>No dose adjustment necessary.</td>
</tr>
</tbody>
</table>
### Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis C Direct Acting Antivirals, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>BIC</td>
<td>↔ BIC expected</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>↔ elbasvir</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ grazoprevir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ DTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ elbasvir and ↑ grazoprevir expected</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ elbasvir</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ grazoprevir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ RAL with elbasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAL AUC ↑ 43% with grazoprevir</td>
<td></td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>BIC</td>
<td>↔ BIC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DTG, RAL</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Glecaprevir AUC ↑ 3-fold</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pibrentasvir AUC ↑ 57%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EVG AUC ↑ 47%</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>EVG/c/TDF/FTC</td>
<td>↑ TDF and ↑ ledipasvir expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>EVG/c/TAF/FTC</td>
<td>↔ EVG/c/TAF/FTC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>BIC, DTG, RAL</td>
<td>↔ DTG or RAL</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ simeprevir expected</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>All INSTIs</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>All INSTIs</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>EVG/c</td>
<td>When Given with Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg: • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td></td>
</tr>
<tr>
<td><strong>Herbal Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>BIC, DTG</td>
<td>↓ BIC and DTG possible</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↓ EVG and COBI possible</td>
<td>Contraindicated.</td>
</tr>
</tbody>
</table>
### Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal Contraceptives Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC, DTG, RAL</td>
<td>↓ ethinyl estradiol, norgestimate, and DTG or RAL</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>Norgestimate AUC, C&lt;sub&gt;max&lt;/sub&gt;, and C&lt;sub&gt;min&lt;/sub&gt; ↑ &gt;2-fold Ethinyl estradiol AUC ↓ 25% and C&lt;sub&gt;min&lt;/sub&gt; ↓ 44%</td>
<td>The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug and consider using an alternative contraceptive method. ↑ drospirenone possible Clinical monitoring is recommended, due to the potential for hyperkalemia.</td>
<td></td>
</tr>
<tr>
<td><strong>Hormonal Contraceptives Non-oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All INSTIs</td>
<td>No data</td>
<td>No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear if oral drug-drug interaction data can be extrapolated beyond oral routes of administration.</td>
<td></td>
</tr>
<tr>
<td><strong>Menopausal Hormone Replacement Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC, DTG, RAL</td>
<td>With Estradiol or Conjugated Estrogen (Equine and Synthetic): • ↔ estrogen expected ↔ drospirenone, medroxyprogesterone, or micronized progesterone expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>↓ estrogen expected</td>
<td>Adjust estrogen and progestin dose as needed based on clinical effects.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ drospirenone possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ oral medroxyprogesterone possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ oral micronized progesterone possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender-Affirming Hormone Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC, DTG, RAL</td>
<td>↔ estrogen expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>BIC, DTG, EVG/c, RAL</td>
<td>↔ finasteride, goserelin, leuprolide acetate, spironolactone expected</td>
<td>Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>↓ estradiol expected</td>
<td>Monitor masculinizing effects of testosterone and for adverse effects and adjust testosterone dose as necessary.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ dutasteride possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>↑ testosterone possible</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>→ expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>Atorvastatin AUC ↑ 2.6-fold and C&lt;sub&gt;max&lt;/sub&gt; ↑ 2.3-fold</td>
<td>Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>→ expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>Significant ↑ lovastatin expected</td>
<td>Contraindicated.</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin, Pravastatin</td>
<td>→ expected</td>
<td>No dose adjustment necessary.</td>
<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>No data</td>
<td>No dose recommendation.</td>
<td></td>
</tr>
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</table>
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs  *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 12 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
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<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HMG-CoA Reductase Inhibitors, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Rosuvastatin AUC ↑ 38% and C&lt;sub&gt;max&lt;/sub&gt; ↑ 89%</td>
<td>Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>Significant ↑ simvastatin expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, Everolimus, Sirolimus, Tacrolimus</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ immunosuppressant possible</td>
<td>Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.</td>
</tr>
<tr>
<td><strong>Narcotics/Treatment for Opioid Dependence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>BIC, DTG</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Sublingual, buccal, or implant</td>
<td>EVG/c</td>
<td>Buprenorphine AUC ↑ 35% and C&lt;sub&gt;min&lt;/sub&gt; ↑ 66%</td>
<td>No dose adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.</td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔ observed (sublingual)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↔ expected (implant)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>All INSTIs</td>
<td>No significant effect</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>PDE5 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avanafil</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>No data</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑ sildenafil expected</td>
<td>For Treatment of Erectile Dysfunction:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For treatment of PAH:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Contraindicated.</td>
</tr>
</tbody>
</table>
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<thead>
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</thead>
<tbody>
<tr>
<td><strong>PDE5 Inhibitors, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ tadalafil expected</td>
<td>For Treatment of Erectile Dysfunction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Start with tadalafil 5-mg dose and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For Treatment of PAH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In Patients on EVG/c &gt;7 Days:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to tadalafil 40 mg once daily based on tolerability.</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ vardenafil expected</td>
<td>Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.</td>
</tr>
<tr>
<td><strong>Sedative/Hypnotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ benzodiazepines possible</td>
<td>Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor. Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam.</td>
</tr>
<tr>
<td>Midazolam, Triazolam</td>
<td>BIC, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td>With DTG 25 mg</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ midazolam AUC</td>
<td>Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c. Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if &gt;1 dose is administered.</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ suvorexant expected</td>
<td>Coadministration is not recommended.</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ zolpidem expected</td>
<td>Initiate zolpidem at a low dose. Dose reduction may be necessary.</td>
</tr>
</tbody>
</table>
Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscellaneous Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcifediol</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ calcifediol possible</td>
<td>Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations should be closely monitored.</td>
</tr>
<tr>
<td>Cisapride</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ cisapride expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Colchicine</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ colchicine expected</td>
<td>Do not coadminister in patients with hepatic or renal impairment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For Treatment of Gout Flares:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Administer colchicine 0.6 mg for 1 dose, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For Prophylaxis of Gout Flares:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If original dose was colchicine 0.6 mg BID, decrease to colchicine 0.3 mg once daily. If regimen was 0.6 mg once daily, decrease to 0.3 mg every other day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For Treatment of Familial Mediterranean Fever:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>DTG</td>
<td>↓ DTG possible</td>
<td>Monitor for ARV efficacy.</td>
</tr>
<tr>
<td>BIC, EVG/c</td>
<td></td>
<td>↓ BIC, EVG/c expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td>↔ expected</td>
<td></td>
</tr>
<tr>
<td>Ergot Derivatives</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ dihydroergotamine, ergotamine, methylergonovine expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ dronabinol possible</td>
<td>Monitor for dronabinol-related adverse effects.</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ eluxadoline possible</td>
<td>Monitor for eluxadoline-related adverse effects.</td>
</tr>
<tr>
<td>Flibanserin</td>
<td>BIC, DTG, RAL</td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td></td>
<td>↑ flibanserin expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>Mitotane</td>
<td>BIC, EVG/c</td>
<td>↑ BIC and ↓ EVG/c expected</td>
<td>Contraindicated.</td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td>↓ DTG possible</td>
<td>Monitor for ARV efficacy.</td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td>↔ expected</td>
<td>No dose adjustment necessary.</td>
</tr>
</tbody>
</table>
### Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs  
(Last updated October 25, 2018; last reviewed October 25, 2018)  
(page 15 of 15)

<table>
<thead>
<tr>
<th>Concomitant Drug Class/Name</th>
<th>INSTI</th>
<th>Effect on INSTI or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
</table>
| **Polyvalent Cation Supplements**  
Mg, Al, Fe, Ca, Zn, including multivitamins with minerals  
**Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids. | BIC | ↔ BIC AUC if given simultaneously with Fe or Ca and food  
BIC AUC ↓ 33% if given simultaneously with CaCO₃ under fasting conditions  
BIC AUC ↓ 63% if given simultaneously with Fe under fasting conditions | With Supplements that Contain Ca or Fe:  
+ BIC and supplements containing Ca or Fe can be taken together with food.  
Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe. |
| DTG | DTG AUC ↓ 39% if given simultaneously with calcium carbonate under fasting conditions  
DTG AUC ↓ 54% if given simultaneously with Fe under fasting conditions  
↔ DTG when administered with Ca or Fe supplement simultaneously with food | With Supplements That Contain Ca or Fe:  
+ DTG and supplements containing Ca or Fe can be taken together with food; alternately, administer DTG at least 2 hours before or at least 6 hours after supplement.  
Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements containing Ca or Fe. |
| EVG/c, RAL | ↓ INSTI possible | If coadministration is necessary, give INSTI at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy.  
Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown. |
| **Salmeterol** | BIC, DTG, RAL | ↔ expected | No dose adjustment necessary.  
Do not coadminister, due to potential increased risk of salmeterol-associated cardiovascular events. |
| EVG/c | ↑ salmeterol possible | |

**Key to Symbols:**  
↑ = increase  
↓ = decrease  
↔ = no change

**Key to Acronyms:**  
Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; Ca = calcium; CaCO₃ = calcium carbonate; CCB = calcium channel blocker; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PK = pharmacokinetic; PTH = parathyroid hormone; RAL = raltegravir; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; Zn = zinc
Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents)  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 1 of 3)

In the table below, “No dose adjustment necessary” indicates that the FDA-approved dose of MVC 300 mg twice daily should be used. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>CCR5 Antagonist</th>
<th>Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>MVC</td>
<td>↓ MVC possible</td>
<td>If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.</td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Consider dose reduction to MVC 150 mg BID.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MVC 150 mg BID</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MVC 150 mg BID</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Consider dose reduction to MVC 150 mg BID.</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MVC 150 mg BID</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>MVC</td>
<td>↓ MVC possible</td>
<td>If used without a strong CYP3A inducer or inhibitor, no dose adjustment is necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If used with a strong CYP3A inhibitor, use MVC 150 mg BID.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>MVC</td>
<td>MVC AUC ↓ 64%</td>
<td>Dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MVC 600 mg BID</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>MVC</td>
<td>↓ MVC expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>Hepatitis C Direct-Acting Antivirals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dasabuvir plus Ombitasvir/Paritaprevir/RTV</td>
<td>MVC</td>
<td>↑ MVC expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Concomitant Drug Class/Name</td>
<td>CCR5 Antagonist</td>
<td>Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations</td>
<td>Dosing Recommendations and Clinical Comments</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Hepatitis C Direct-Acting Antivirals, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Herbal Products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>MVC</td>
<td>↓ MVC expected</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td><strong>Hormonal Therapies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal Contraceptives</td>
<td>MVC</td>
<td>↔ Ethinyl estradiol or levonorgestrel</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Menopausal Hormone Replacement Therapy</td>
<td>MVC</td>
<td>↔ MVC or hormone replacement therapies expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Gender-Affirming Hormone Therapies</td>
<td>MVC</td>
<td>↔ MVC or gender-affirming hormones expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>ARV Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INSTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC, DTG</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EVG/c</td>
<td>MVC</td>
<td>↑ MVC possible</td>
<td>Dose: • MVC 150 mg BID</td>
</tr>
<tr>
<td>RAL</td>
<td>MVC</td>
<td>MVC AUC ↓ 21% RAL AUC ↓ 37%</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR, RPV</td>
<td>MVC</td>
<td>↔ MVC expected</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>EFV</td>
<td>MVC</td>
<td>MVC AUC ↓ 45%</td>
<td>Dose: • MVC 600 mg BID</td>
</tr>
<tr>
<td>ETR</td>
<td>MVC</td>
<td>MVC AUC ↓ 53%</td>
<td>Dose: • MVC 600 mg BID in the absence of a potent CYP3A inhibitor</td>
</tr>
<tr>
<td>NVP</td>
<td>MVC</td>
<td>↔ MVC AUC</td>
<td>Without HIV PI: • MVC 300 mg BID With HIV PI (Except TPV/r): • MVC 150 mg BID</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV with or without RTV or COBI</td>
<td>MVC</td>
<td>With Unboosted ATV: • MVC AUC ↑ 257% With (ATV/r 300 mg/100 mg) Once Daily: • MVC AUC ↑ 388%</td>
<td>Dose: • MVC 150 mg BID</td>
</tr>
</tbody>
</table>
### Concomitant Drug Class/ Name
### CCR5 Antagonist
### Effect on CCR5 Antagonist and/or ConcomitantDrug Concentrations
### Dosing Recommendations and Clinical Comments

#### PIs, continued

<table>
<thead>
<tr>
<th>Concomitant Drug Class/ Name</th>
<th>CCR5 Antagonist</th>
<th>Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
</table>
| **DRV/c or DRV/r** | MVC | With (DRV/r 600 mg/100 mg) BID:  
• MVC AUC ↑ 305%  
With (DRV/r 600 mg/100 mg) BID and ETR:  
• MVC AUC ↑ 210% | Dose:  
• MVC 150 mg BID |
| **LPV/r** | MVC | MVC AUC ↑ 295%  
With LPV/r and EFV:  
• MVC AUC ↑ 153% | Dose:  
• MVC 150 mg BID |
| **RTV** | MVC | With RTV 100 mg BID:  
• MVC AUC ↑ 161% | Dose:  
• MVC 150 mg BID |
| **TPV/r** | MVC | With (TPV/r 500 mg/200 mg) BID:  
• ↔ MVC AUC | No dose adjustment necessary. |

**Key to Symbols:**

↑ = increase  
↓ = decrease  
↔ = no change

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir.
Table 20a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 1 of 2)

**Note:** Delavirdine (DLV), fosamprenavir (FPV), indinavir (IDV), nelfinavir (NFV), and saquinavir (SQV) are not included in this table. Please refer to the Food and Drug Administration product labels for DLV, FPV, IDV, NFV, and SQV for information regarding drug interactions.

<table>
<thead>
<tr>
<th>Pls</th>
<th>NNRTIs</th>
<th>DOR</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPVa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unboosted PK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ DOR expected</td>
<td>↔ EFV</td>
<td>ATV AUC ↓ 74%</td>
<td>ETR AUC ↑ 50% and Cmin ↑ 58%</td>
<td>↓ ATV possible</td>
<td>↑ RPV possible</td>
</tr>
<tr>
<td></td>
<td>↔ ATV expected</td>
<td></td>
<td></td>
<td>ATVP AUC ↓ 17% and Cmin ↓ 47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ DOR expected</td>
<td>↓ ATV possible</td>
<td>↓ ATV possible</td>
<td>ETR AUC ↑ 50% and Cmin ↑ 58%</td>
<td>↓ ATV possible</td>
<td>↑ RPV possible</td>
</tr>
<tr>
<td></td>
<td>↔ ATV expected</td>
<td></td>
<td></td>
<td>ATVP AUC ↓ 17% and Cmin ↓ 47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td></td>
</tr>
<tr>
<td><strong>ATV/c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ DOR expected</td>
<td>↓ ATV possible</td>
<td>↓ ATV possible</td>
<td>ETR AUC ↑ 50% and Cmin ↑ 58%</td>
<td>↓ ATV possible</td>
<td>↑ RPV possible</td>
</tr>
<tr>
<td></td>
<td>↔ ATV expected</td>
<td></td>
<td></td>
<td>ATVP AUC ↓ 17% and Cmin ↓ 47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td></td>
</tr>
<tr>
<td><strong>ATV/r</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ DOR expected</td>
<td>(ATV 400 mg plus RTV 100 mg) Once Daily</td>
<td>(ATV 300 mg plus RTV 100 mg) Once Daily</td>
<td>ETR 400 mg Once Daily</td>
<td>↓ DRV possible</td>
<td>↑ DRV expected</td>
</tr>
<tr>
<td></td>
<td>↔ ATV expected</td>
<td>(ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV)</td>
<td>(ATV 300 mg plus RTV 100 mg) Once Daily</td>
<td>(ATV 300 mg plus RTV 100 mg) Once Daily</td>
<td>↓ DRV possible</td>
<td>↑ DRV expected</td>
</tr>
<tr>
<td>Standard doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td></td>
</tr>
<tr>
<td><strong>DRV/c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PK Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ DOR expected</td>
<td>↓ DRV possible</td>
<td>ETR 400 mg Once Daily with (DRV 800 mg plus COBI 150 mg) Once Daily</td>
<td>↓ DRV possible</td>
<td>↔ DRV expected</td>
<td>↑ DRV expected</td>
</tr>
<tr>
<td></td>
<td>↔ DRV expected</td>
<td>↓ COBI possible</td>
<td>(ATV 300 mg plus RTV 100 mg) once daily</td>
<td>(ATV 300 mg plus RTV 100 mg) Once Daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td></td>
</tr>
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</table>
### Table 20a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018)

<table>
<thead>
<tr>
<th>Pls</th>
<th>PK Data</th>
<th>DOR</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPV&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV/r</td>
<td>↑ DOR expected</td>
<td>With (DRV 300 mg plus RTV 100 mg) BID:</td>
<td>ETR 100 mg BID with (DRV 600 mg plus RTV 100 mg) BID:</td>
<td>With (DRV 400 mg plus RTV 100 mg) BID:</td>
<td>With (DRV 150 mg Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily:</td>
<td>RPV 150 mg Once Daily</td>
</tr>
<tr>
<td>Data</td>
<td>↔ DRV expected</td>
<td>• EFV AUC ↑ 21% and C&lt;sub&gt;min&lt;/sub&gt; ↓ 31%</td>
<td>• ETR AUC ↓ 37% and C&lt;sub&gt;min&lt;/sub&gt; ↓ 49%</td>
<td>• NVP AUC ↑ 27% and C&lt;sub&gt;min&lt;/sub&gt; ↑ 47%</td>
<td>• DRV AUC ↑ 24%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• RPV AUC ↑ 130% and C&lt;sub&gt;min&lt;/sub&gt; ↑ 178%</td>
</tr>
<tr>
<td>Dose</td>
<td>Standard doses</td>
<td>Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.</td>
<td>Standard doses</td>
<td>Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.</td>
<td>Standard doses</td>
<td>Standard doses</td>
</tr>
<tr>
<td>LPV/r</td>
<td>↑ DOR expected</td>
<td>With LPV/r Tablets 500 mg/125 mg&lt;sup&gt;c&lt;/sup&gt; BID:</td>
<td>With LPV/r Tablets:</td>
<td>With LPV/r Capsules:</td>
<td>RPV 150 mg Once Daily</td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td>↔ LPV expected</td>
<td>• LPV concentration similar to that of LPV/r 400 mg/100 mg BID without EFV</td>
<td>• ETR AUC ↓ 35% (comparable to the decrease with DRV/r)</td>
<td>• LPV AUC</td>
<td>• RPV AUC ↓ 52% and C&lt;sub&gt;min&lt;/sub&gt; ↓ 74%</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Standard doses</td>
<td>LPV/r tablets 500 mg/125 mg&lt;sup&gt;c&lt;/sup&gt; BID; LPV/r oral solution 533 mg/133 mg BID</td>
<td>Standard doses</td>
<td>LPV/r tablets 500 mg/125 mg&lt;sup&gt;c&lt;/sup&gt; BID; LPV/r oral solution 533 mg/133 mg BID</td>
<td>Standard doses</td>
<td></td>
</tr>
<tr>
<td>TPV/r</td>
<td>↑ DOR expected</td>
<td>With (TPV 500 mg plus RTV 100 mg) BID:</td>
<td>With (TPV 500 mg plus RTV 200 mg) BID:</td>
<td>With (TPV 250 mg plus RTV 200 mg) BID or with (TPV 750 mg plus RTV 100 mg) BID:</td>
<td>↑ RPV possible</td>
<td></td>
</tr>
<tr>
<td>Always use TPV with RTV</td>
<td>↔ TPV expected</td>
<td>• ↔ EFV</td>
<td>• ↔ ETR AUC 76% and C&lt;sub&gt;min&lt;/sub&gt; 82%</td>
<td>• ↔ NVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td>Standard doses</td>
<td>• TPV AUC ↓ 31% and C&lt;sub&gt;min&lt;/sub&gt; ↓ 42%</td>
<td>• ↔ TPV AUC and C&lt;sub&gt;min&lt;/sub&gt; ↑ 24%</td>
<td>• ↔ TPV expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Approved dose for RPV is 25 mg once daily. Most PK studies were performed using RPV 75 mg to 150 mg per dose.

<sup>b</sup> DRV concentration was compared to a historic control.

<sup>c</sup> Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

**Key to Symbols:**
- ↑ = increase
- ↓ = decrease
- ↔ = no change

**Key to Acronyms:**
- ART = antiretroviral therapy
- ATV = atazanavir
- ATV/c = atazanavir/cobicistat
- ATV/r = atazanavir/ritonavir
- AUC = area under the curve
- BID = twice daily
- C<sub>min</sub> = minimum plasma concentration
- COBI = cobicistat
- DOR = doravirine
- DRV = darunavir
- DRV/c = darunavir/cobicistat
- DRV/r = darunavir/ritonavir
- EFV = efavirenz
- ETR = etravirine
- LPV = lopinavir
- LPV/r = lopinavir/ritonavir
- NNRTI = non-nucleoside reverse transcriptase inhibitor
- NVP = nevirapine
- PI = protease inhibitor
- PK = pharmacokinetic
- RPV = rilpivirine
- RTV = ritonavir
- TPV = tipranavir
- TPV/r = tipranavir/ritonavir
Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors  *(Last updated October 25, 2018; last reviewed October 25, 2018)* (page 1 of 3)

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

<table>
<thead>
<tr>
<th>ARV Drugs by Drug Class</th>
<th>INSTIs</th>
<th>BIC</th>
<th>DTG</th>
<th>EVG/c</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>PK</td>
<td>↔ DOR, BIC expected</td>
<td>↔ DOR</td>
<td>↑ DOR expected</td>
<td>↔ DOR, RAL expected</td>
</tr>
<tr>
<td></td>
<td>Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
<td>Standard doses</td>
</tr>
<tr>
<td>EFV</td>
<td>PK</td>
<td>↓ BIC expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Do not coadminister</td>
<td>In Patients Without INSTI Resistance:</td>
<td>Do not coadminister.</td>
<td>Standard doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETR</td>
<td>PK</td>
<td>↓ BIC expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td></td>
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</tr>
</tbody>
</table>

*ARV Drugs by Drug Class: INSTIs (Integrase Strand Transfer Inhibitors) and NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors)*

**Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.**

**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018)** (page 1 of 3)

**Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.**

**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018)** (page 1 of 3)

**Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.**

**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018)** (page 1 of 3)

**Recommendations for managing a particular drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.**
<table>
<thead>
<tr>
<th>ARV Drugs by Drug Class</th>
<th>INSTIs</th>
<th>NNRTIs, continued</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIC</td>
<td>DTG</td>
</tr>
<tr>
<td>ETR, continued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Do not coadminister.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>PK Data</td>
<td>↓ BIC expected</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>RPV</td>
<td>PK Data</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Standard doses</td>
</tr>
<tr>
<td>Pls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/c</td>
<td>PK Data</td>
<td>BIC AUC ↑ 305%</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>ATV +/- RTV</td>
<td>PK Data</td>
<td>BIC AUC ↑ 310%</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/c</td>
<td>PK Data</td>
<td>BIC AUC ↑ 74%</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard doses</td>
</tr>
</tbody>
</table>

Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 3)
Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors  

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

(page 3 of 3)

<table>
<thead>
<tr>
<th>ARV Drugs by Drug Class</th>
<th>INSTIs</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIC</td>
<td>DTG</td>
<td>EVG/c</td>
<td>RAL</td>
</tr>
<tr>
<td>PKs, continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| PK Data | No data | (DRV 600 mg plus RTV 100 mg) BID with DTG 30 mg Once Daily:  
• DTG AUC ↓ 22% and C_min ↓ 38% | ↑ or ↓ EVG, COBI, DRV possible | With (DRV 600 mg plus RTV 100 mg) BID:  
• RAL AUC ↓ 29% and C_min ↑ 38% |
| Dose | Standard doses | Standard doses | Do not coadminister. | Standard doses |
| PK Data | No data | With (LPV 400 mg plus RTV 100 mg) BID and DTG 30 mg Once Daily:  
• ↔ DTG | ↑ or ↓ EVG, COBI, LPV possible  
RTV and COBI have similar effects on CYP3A. | ↓ RAL  
↔ LPV/r |
| Dose | Consider alternative combination. | Standard doses | Do not coadminister. | Standard doses |
| PK Data | ↓ BIC possible | With (TPV 500 mg plus RTV 200 mg) BID and DTG 50 mg Once Daily:  
• DTG AUC ↓ 59% and C_min ↓ 76% | ↑ or ↓ EVG, COBI, TPV possible  
RTV and COBI have similar effects on CYP3A. | With (TPV 500 mg plus RTV 200 mg) BID and RAL 400 mg BID:  
• RAL AUC ↓ 24% and C_min ↓ 55% |
| Dose | Do not coadminister. | In Patients Without INSTI Resistance:  
• DTG 50 mg BID | Do not coadminister. | RAL 400 mg BID  
Coadministration with RAL 1200 mg once daily is not recommended. |
| In Patients With Certain INSTI-Associated Resistance or Clinically Suspected INSTI Resistance:  
• Consider alternative combination. | | | |

* Refer to DTG product labeling for details.

**Key to Symbols:**  
↑ = increase  
↓ = decrease  
↔ = no change

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BIC = bictegravir; BID = twice daily; C_min = minimum plasma concentration; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpirivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

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Conclusion  (Last updated January 28, 2016; last reviewed January 28, 2016)

The Panel has carefully reviewed results from clinical HIV therapy trials and considered how they affect appropriate care guidelines. HIV care is complex and rapidly evolving. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. Absent such evidence, the Panel has attempted to base recommendations on reasonable options for HIV care.

HIV care requires partnerships and open communication. Guidelines are only a starting point for medical decision making involving informed providers and patients. Although guidelines can identify some parameters of high-quality care, they cannot substitute for sound clinical judgment.

As further research is conducted and reported, these guidelines will be modified. The Panel anticipates continued progress in refining antiretroviral therapy regimens and strategies. The Panel hopes these guidelines are useful and is committed to their continued revision and improvement.
## Drug Name Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>abacavir</td>
</tr>
<tr>
<td>APV</td>
<td>amprenavir</td>
</tr>
<tr>
<td>ATV</td>
<td>atazanavir</td>
</tr>
<tr>
<td>BIC</td>
<td>bicitravir</td>
</tr>
<tr>
<td>COBI or c</td>
<td>cobicistat</td>
</tr>
<tr>
<td>d4T</td>
<td>stavudine</td>
</tr>
<tr>
<td>ddI</td>
<td>didanosine</td>
</tr>
<tr>
<td>DLV</td>
<td>delavirdine</td>
</tr>
<tr>
<td>DOR</td>
<td>doravirine</td>
</tr>
<tr>
<td>DRV</td>
<td>darunavir</td>
</tr>
<tr>
<td>DTG</td>
<td>dolutegravir</td>
</tr>
<tr>
<td>EFV</td>
<td>efavirenz</td>
</tr>
<tr>
<td>ETR</td>
<td>etravirine</td>
</tr>
<tr>
<td>EVG</td>
<td>elvitegravir</td>
</tr>
<tr>
<td>FPV</td>
<td>fosamprenavir</td>
</tr>
<tr>
<td>FTC</td>
<td>emtricitabine</td>
</tr>
<tr>
<td>IBA</td>
<td>ibalizumab</td>
</tr>
<tr>
<td>IDV</td>
<td>indinavir</td>
</tr>
<tr>
<td>LPV</td>
<td>lopinavir</td>
</tr>
<tr>
<td>MVC</td>
<td>maraviroc</td>
</tr>
<tr>
<td>NFV</td>
<td>nelfinavir</td>
</tr>
<tr>
<td>NVP</td>
<td>nevirapine</td>
</tr>
<tr>
<td>RAL</td>
<td>raltegravir</td>
</tr>
<tr>
<td>RPV</td>
<td>rilpivirine</td>
</tr>
<tr>
<td>RTV or r</td>
<td>ritonavir</td>
</tr>
<tr>
<td>SQV</td>
<td>saquinavir</td>
</tr>
<tr>
<td>T-20</td>
<td>enfuvirtide</td>
</tr>
<tr>
<td>TAF</td>
<td>tenofovir alafenamide</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>TPV</td>
<td>tipranavir</td>
</tr>
<tr>
<td>ZDV</td>
<td>zidovudine</td>
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## General Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-BMP</td>
<td>beclomethasone 17-monopropionate</td>
</tr>
<tr>
<td>ADAP</td>
<td>AIDS drug assistance program</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Ag/Ab</td>
<td>antigen/antibody</td>
</tr>
<tr>
<td>Al</td>
<td>aluminum</td>
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<td>CCB</td>
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<td>CD4 T lymphocyte</td>
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<td>CDC</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>DHA</td>
<td>dihydroartemisinin</td>
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<td>DILI</td>
<td>drug-induced liver injury</td>
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<td>DMPA</td>
<td>depot medroxyprogesterone acetate</td>
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<td>DOT</td>
<td>directly observed therapy</td>
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</table>

*Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*  
N-2  
Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 1/1/2019
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>EBV</td>
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<td>EC</td>
<td>enteric coated</td>
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<td>electrocardiogram</td>
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<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FDC</td>
<td>fixed-dose combination</td>
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<td>Fe</td>
<td>iron</td>
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<td>FI</td>
<td>fusion inhibitor</td>
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<td>FUL</td>
<td>federal upper limit</td>
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<td>GAZT</td>
<td>azidothymidine glucuronide</td>
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<td>hepatitis B surface antibody</td>
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<td>Kaposi’s sarcoma</td>
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<td>LLOD</td>
<td>lower limits of detection</td>
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<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>MAC</td>
<td><em>Mycobacterium avium</em> complex</td>
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<td>multidrug and toxin extrusion transporter</td>
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<td>Mg</td>
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<td>myocardial infarction</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>multi-tablet regimen</td>
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<td>Na</td>
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<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor</td>
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<tr>
<td>NRTI</td>
<td>nucleoside/nucleotide reverse transcriptase inhibitor</td>
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<td>organic anion-transporting polypeptide</td>
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<td>OCT2</td>
<td>organic cation transporter 2</td>
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<td>OH-itraconazole</td>
<td>active metabolite of itraconazole</td>
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<td>OI</td>
<td>opportunistic infection</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>cobicistat-boosted protease inhibitor</td>
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<td>every (n) hours</td>
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<td>relative risk</td>
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<td>reverse transcriptase</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>STR</td>
<td>single-tablet regimen</td>
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<td>TDM</td>
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<td>triglyceride</td>
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<td>TID</td>
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### Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors

**Last updated October 25, 2018; last reviewed October 25, 2018**

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulations</th>
<th>Dosing Recommendationsa</th>
<th>Elimination/ Metabolic Pathway</th>
<th>Serum/ Intracellular Half-Lives</th>
<th>Adverse Eventsb</th>
</tr>
</thead>
</table>
| **Abacavir** (ABC) | Ziagen | • 300 mg tablet  
• 20 mg/mL oral solution | Ziagen:  
• 600 mg once daily, or  
• 300 mg BID  
Take without regard to meals. | Metabolized by alcohol dehydrogenase and glucuronyl transferase  
Renal excretion of metabolites: 82%  
Dose adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 8). | 1.5 hours/ 12–26 hours |  
• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC.  
• For patients with a history of HSR, re challenge is not recommended.  
• Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath.  
• Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies. |
| **(ABC/3TC)** Epzicom | Note: Generic formulation is available. | Epzicom:  
• (ABC 600 mg plus 3TC 300 mg) tablet  
Epzicom:  
• 1 tablet once daily | | | |
| **(ABC/DTG/3TC)** Triumeq | Note: Generic formulation is available. | Triumeq:  
• (ABC 600 mg plus 3TC 300 mg plus DTG 50 mg) tablet  
Triumeq:  
• 1 tablet once daily | | | |
| **(ABC/ZDV/3TC)** Trizivir | Note: Generic formulation is available. | Trizivir:  
• (ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg) tablet  
Trizivir:  
• 1 tablet BID | | | |
| **Didanosine** (ddI) | Videx  
Videx EC | Videx EC:  
• 125, 200, 250, and 400 mg capsules  
Videx:  
• 10 mg/mL oral solution | Body Weight ≥60 kg:  
• ddI 400 mg once daily  
*With TDF:*  
• ddI 250 mg once daily  
Body Weight <60 kg:  
• ddI 250 mg once daily  
*With TDF:*  
• ddI 200 mg once daily  
Take 1/2 hour before or 2 hours after a meal.  
**Note:** Preferred dosing with oral solution is BID (with the total daily dose divided into 2 doses). | Renal excretion: 50%  
Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8). | 1.5 hours/ >20 hours |  
• Pancreatitis  
• Peripheral neuropathy  
• Retinal changes, optic neuritis  
• Lactic acidosis with hepatic steatosis with or without pancreatitis (rare but potentially life-threatening toxicity)  
• Nausea, vomiting  
• Potential association with noncirrhotic portal hypertension; in some cases, patients presented with esophageal varices  
• One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies.  
• Insulin resistance/diabetes mellitus |
### Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 6)

| Generic Name (Abbreviation) | Formulations | Dosing Recommendations | Elimination/Metabolic Pathway | Serum/Intracellular Half-Lives | Adverse Events
|-----------------------------|--------------|------------------------|--------------------------------|-----------------------------|---------------------|
| **Emtricitabine** (FTC) Emtriva | Emtriva:  
• 200 mg hard gelatin capsule  
• 10 mg/mL oral solution | Emtriva  
Capsule:  
• FTC 200 mg once daily  
Oral Solution:  
• FTC 240 mg (24 mL) once daily  
Take without regard to meals. | Renal excretion: 86%  
Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8). | 10 hours/ >20 hours | • Minimal toxicity  
• Hyperpigmentation/skin discoloration  
• Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue FTC.

**Emtriva**:  
• FTC 200 mg once daily

**Oral Solution**:  
• FTC 240 mg (24 mL) once daily

| (FTC/TAF) Descovy | Descovy:  
• (FTC 200 mg plus TAF 25 mg) tablet | Descovy:  
• 1 tablet once daily |
|-------------------|------------------------|---------------------|
| **Truvada**:  
• (FTC 200 mg plus TAF 25 mg) tablet | Truvada:  
• 1 tablet once daily |
| **(FTC/BIC/TAF) Biktarvy** | Biktarvy:  
• (FTC 200 mg plus BIC 50 mg plus TAF 25 mg) tablet | Biktarvy:  
• 1 tablet once daily |
| **(FTC/DRV/c/TAF) Symtuza** | Symtuza:  
• (FTC 200 mg plus DRV 800 mg plus COBI 150 mg plus TAF 10 mg) tablet | Symtuza:  
• 1 tablet once daily with food |
| **Atripla**:  
• (FTC 200 mg plus EFV 600 mg plus TDF 300 mg) tablet | Atripla:  
• 1 tablet once daily on an empty stomach, preferably at bedtime |
| **Genvoya**:  
• (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg) tablet | Genvoya:  
• 1 tablet once daily with food |
| **Stravid**:  
• (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet | Stravid:  
• 1 tablet once daily with a meal |
| **Complera**:  
• (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet | Complera:  
• 1 tablet once daily with a meal |
### Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 3 of 6)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulations</th>
<th>Dosing Recommendations</th>
<th>Elimination/ Metabolic Pathway</th>
<th>Serum/ Intracellular Half-Lives</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **Lamivudine (3TC) Epivir** | • 150 and 300 mg tablets  
• 10 mg/mL oral solution | Epivir:  
• 3TC 300 mg once daily, or  
• 3 TC 150 mg BID | Renal excretion: 70%  
Dose adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 8). | 5–7 hours/ 18–22 hours | • Minimal toxicity  
• Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue 3TC. |
| **(3TC/ABC) Epzicom** |  |  |  |  |  |
| **(3TC/TDF) Cimduo** |  |  |  |  |  |
| **(3TC/ZDV) Combivir** |  |  |  |  |  |
| **(3TC/ABC/ZDV) Trizivir** |  |  |  |  |  |
| **(3TC/DOR/TDF) Delstrigo** |  |  |  |  |  |
| **(3TC/DTG/ABC) Triumeq** |  |  |  |  |  |
| **(3TC/EFV/TDF) Symfi** |  |  |  |  |  |
| **(3TC/EFV/TDF) Symfi Lo** |  |  |  |  |  |
### Stavudine (d4T)

**Trade Name:** Zerit

**Formulations:**
- 15, 20, 30, and 40 mg capsules
- 1 mg/mL oral solution

**Dosing Recommendations**: 
- **Body Weight ≥60 kg:**
  - d4T 40 mg BID
- **Body Weight <60 kg:**
  - d4T 30 mg BID

*Note:* WHO recommends 30 mg BID dosing regardless of body weight.

**Elimination/Metabolic Pathway:**
- Renal excretion: 50%

**Serum/Intracellular Half-Lives:**
- 1 hour/7.5 hours

**Adverse Events**:
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatic steatosis
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness

**Renal Insufficiency:**
- Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).

**Note:** Available as a 25-mg tablet for the treatment of HBV.

### Tenofovir Alafenamide (TAF) (Vemlidy)

**Note:** Available as a 25-mg tablet for the treatment of HBV.

**Formulations:**
See FDCs for HIV treatment below.

**Dosing:**
- **Body Weight ≥100 kg:**
  - TAF 25 mg BID

**Elimination/Metabolic Pathway:**
- Metabolized by cathepsin A.

**Serum/Intracellular Half-Lives:**
- 0.5 hours/150–180 hours

**Adverse Events**:
- Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy are less likely to occur with TAF than with TDF.
- Osteomalacia, decrease in bone mineral density are less likely to occur with TAF than with TDF.
- Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue TAF.
- Diarrhea, nausea, headache

**Note:** Available as a 25-mg tablet for the treatment of HBV.
## Generic Name (Abbreviation) Trade Name

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulations</th>
<th>Dosing Recommendations</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum/Intracellular Half-Lives</th>
<th>Adverse Events</th>
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<tr>
<td>Tenofovir Disoproxil Fumurate (TDF) Viread</td>
<td>Viread: • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder</td>
<td>Viread: • TDF 300 mg once daily, or • 7.5 level scoops of oral powder once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1g of oral powder). • Take without regard to meals.</td>
<td>Renal excretion is primary route of elimination. Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 8).</td>
<td>17 hours/ &gt;60 hours</td>
<td>• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy • Osteomalacia, decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence</td>
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<td>Generic: • 300 mg tablet</td>
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<td>(TDF/3TC) Cimduo</td>
<td>Cimduo: • (TDF 300 mg plus 3TC 300 mg) tablet</td>
<td>Cimduo: • 1 tablet once daily</td>
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<td>(TDF/FTC) Truvada</td>
<td>Truvada: • (TDF 300 mg plus FTC 200 mg tablet)</td>
<td>Truvada: • 1 tablet once daily • Take without regard to meals.</td>
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<td>Delstrigo: • (TDF 300 mg plus DOR 100 mg plus 3TC 300 mg) tablet</td>
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<tr>
<td>(TDF/EVF/FTC) Atripla</td>
<td>Atripla: • (TDF 300 mg plus EFV 600 mg plus FTC 200 mg) tablet</td>
<td>Atripla: • 1 tablet once daily on an empty stomach, preferably at bedtime</td>
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<td>(TDF/EVF/3TC) Symfi</td>
<td>Symfi: • (TDF 300 mg plus EFV 600 mg plus 3TC 300 mg) tablet</td>
<td>Symfi: • 1 tablet once daily on an empty stomach, preferably at bedtime</td>
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<tr>
<td>(TDF/EVF/3TC) Symfi Lo</td>
<td>Symfi Lo: • (TDF 300 mg plus EFV 400 mg plus 3TC 300 mg) tablet</td>
<td>Symfi Lo: • 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TDF/EVG/c/FTC) Stribild</td>
<td>Stribild: • (TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet</td>
<td>Stribild: • 1 tablet once daily • Take with food.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TDF/RPV/FTC) Complera</td>
<td>Complera: • (TDF 300 mg plus RPV 25 mg plus FTC 200 mg) tablet</td>
<td>Complera: • 1 tablet once daily • Take with a meal.</td>
<td></td>
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<td></td>
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</tbody>
</table>
Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors  
(Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 6)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulations</th>
<th>Dosing Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum/Intracellular Half-Lives</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zidovudine (ZDV) Retrovir</strong> Note: Generic is available.</td>
<td>Retrovir: • 100 mg capsule • 300 mg tablet (only available as generic) • 10 mg/mL intravenous solution • 10 mg/mL oral solution</td>
<td>Retrovir: • ZDV 300 mg BID, or • ZDV 200 mg TID • Take without regard to meals.</td>
<td>Metabolized to GAZT Renal excretion of GAZT</td>
<td>1.1 hours/7 hours</td>
<td>• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy</td>
</tr>
<tr>
<td><strong>(ZDV/3TC) Combivir</strong> Note: Generic is available.</td>
<td>Combivir: • (ZDV 300 mg plus 3TC 150 mg) tablet</td>
<td>Combivir: • 1 tablet BID • Take without regard to meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(ZDV/3TC/ABC) Trizivir</strong> Note: Generic is available.</td>
<td>Trizivir: • (ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg) tablet</td>
<td>Trizivir: • 1 tablet BID • Take without regard to meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 8.

<sup>b</sup> Also see Table 15.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddl = didanosine; DOR = doravirine; DRV = darunavir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine
### Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors

*(Last updated October 25, 2018; last reviewed October 25, 2018)*

**Note:** DLV is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
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<th>Dosing Recommendations</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doravirine</strong>&lt;br&gt;(DOR)</td>
<td>Pifeltro</td>
<td>Pifeltro:&lt;br&gt;• 100 mg tablet&lt;br&gt;• 1 tablet once daily</td>
<td>CYP3A4/5 substrate</td>
<td>15 hours</td>
<td>• Nausea&lt;br&gt;• Dizziness&lt;br&gt;• Abnormal dreams</td>
<td></td>
</tr>
<tr>
<td><strong>(DOR/TDF/3TC)</strong></td>
<td>Delstrigo</td>
<td>Delstrigo:&lt;br&gt;• (DOR 100 mg plus TDF 300 mg plus 3TC 300 mg) tablet&lt;br&gt;• 1 tablet once daily</td>
<td>Metabolized by CYPs 2B6 (primary), 3A4, and 2A6&lt;br&gt;CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer</td>
<td>40–55 hours</td>
<td>• Rash&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;• Neuropsychiatric symptoms&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;• Increased transaminase levels&lt;br&gt;• Hyperlipidemia&lt;br&gt;• False-positive results with some cannabinoid and benzodiazepine screening assays reported&lt;br&gt;• QT interval prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz</strong>&lt;br&gt;(EFV)</td>
<td>Sustiva</td>
<td>Sustiva:&lt;br&gt;• 50 and 200 mg capsules&lt;br&gt;• 600 mg tablet&lt;br&gt;• 600 mg tablet</td>
<td>CYP3A4, 2C9, and 2C19 inhibitor (more an inducer than an inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer</td>
<td>40–55 hours</td>
<td>• Rash&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;• Neuropsychiatric symptoms&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;• Increased transaminase levels&lt;br&gt;• Hyperlipidemia&lt;br&gt;• False-positive results with some cannabinoid and benzodiazepine screening assays reported&lt;br&gt;• QT interval prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>(EFV/TDF/FTC)</strong></td>
<td>Atripla</td>
<td>Atripla:&lt;br&gt;• (EFV 600 mg plus TDF 300 mg plus FTC 200 mg) tablet&lt;br&gt;• 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td>• Rash, including Stevens-Johnson syndrome&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;• HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported.&lt;br&gt;• Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(EFV/TDF/3TC)</strong></td>
<td>Symfi</td>
<td>Symfi:&lt;br&gt;• (EFV 600 mg plus TDF 300 mg plus 3TC 300 mg) tablet&lt;br&gt;• 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td>3A4 inducer; 2C9 and 2C19 inhibitor&lt;br&gt;CYP3A4, 2C9, and 2C19 substrate</td>
<td>41 hours</td>
<td>• Rash, including Stevens-Johnson syndrome&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;• HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported.&lt;br&gt;• Nausea</td>
<td></td>
</tr>
<tr>
<td><strong>(EFV/TDF/3TC)</strong></td>
<td>Symfi Lo</td>
<td>Symfi Lo:&lt;br&gt;• (EFV 400 mg plus TDF 300 mg plus 3TC 300 mg) tablet&lt;br&gt;• 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td>3A4 inducer; 2C9 and 2C19 inhibitor&lt;br&gt;CYP3A4, 2C9, and 2C19 substrate</td>
<td>41 hours</td>
<td>• Rash, including Stevens-Johnson syndrome&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;• HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported.&lt;br&gt;• Nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Etravirine</strong>&lt;br&gt;(ETR)</td>
<td>Intelence</td>
<td>Intelence:&lt;br&gt;• 25, 100, and 200 mg tablets&lt;br&gt;• 200 mg BID&lt;br&gt;• Take following a meal.</td>
<td>3A4 inducer; 2C9 and 2C19 inhibitor&lt;br&gt;CYP3A4, 2C9, and 2C19 substrate</td>
<td>41 hours</td>
<td>• Rash, including Stevens-Johnson syndrome&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;• HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported.&lt;br&gt;• Nausea</td>
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</table>
### Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors  (Last updated October 25, 2018; last reviewed October 25, 2018)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulations</th>
<th>Dosing Recommendations</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Nevirapine (NVP) Viramune or Viramune XR | • 200 mg tablet  
• 400 mg XR tablet  
• 50 mg/5 mL oral suspension | • 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily  
• Take without regard to meals.  
• Repeat lead-in period if therapy is discontinued for >7 days.  
• In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves, but do not administer for longer than 28 days total. | CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces | 25–30 hours | Rash, including Stevens-Johnson syndrome | **Note**: Generic is available for 200 mg tablets and oral suspension. |

**Contraindicated in patients with moderate to severe hepatic impairment.** Dose adjustment is recommended in patients on hemodialysis (see Appendix B, Table 8). |

| Rilpivirine (RPV) Edurant | Edurant:  
• 25 mg tablet | Edurant:  
• 25 mg once daily  
• Take with a meal. | CYP3A4 substrate | 50 hours | Rash  
• Depression, insomnia, headache  
• Hepatotoxicity  
• QT interval prolongation |

| (RPV/DTG) Juluca | Juluca:  
• (RPV 25 mg plus DTG 50 mg) tablet | Juluca:  
• 1 tablet once daily  
• Take with a meal. |  |  |  |

| (RPV/TAF/FTC) Odefsey | Odefsey:  
• (RPV 25 mg plus TAF 25 mg plus FTC 200 mg) tablet | Odefsey:  
• 1 tablet once daily  
• Take with a meal. |  |  |  |

| (RPV/TDF/FTC) Complera | Complera:  
• (RPV 25 mg plus TDF 300 mg plus FTC 200 mg) tablet | Complera:  
• 1 tablet once daily  
• Take with a meal. |  |  |  |

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* For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 8.  
* Also see Table 15.  
* Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.  
* Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.  
* **Key to Acronyms:** 3TC = lamivudine; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release
### Appendix B, Table 3. Characteristics of Protease Inhibitors

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

*Last updated October 25, 2018; last reviewed October 25, 2018*

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
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<th>Dosing Recommendations</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **Atazanavir** (ATV) Reyataz | Reyataz:  
- 150, 200, and 300 mg capsules  
- 50 mg single packet oral powder | In ARV-Naive Patients:  
- (ATV 300 mg plus RTV 100 mg) once daily; or  
- ATV 400 mg once daily  
With TDF or in ARV-Experienced Patients:  
- (ATV 300 mg plus RTV 100 mg) once daily  
With EFV in ARV-Naive Patients:  
- (ATV 400 mg plus RTV 100 mg) once daily  
Take with food.  
For dosing recommendations with H2 antagonists and PPIs, refer to Table 19a. | CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor  
Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8).  
7 hours | • Indirect hyperbilirubinemia  
• PR interval prolongation:  
First degree symptomatic AV block reported. Use with caution in patients who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation.  
• Hyperglycemia  
• Fat maldistribution  
• Cholelithiasis  
• Nephrolithiasis  
• Renal insufficiency  
• Serum transaminase elevations  
• Hyperlipidemia (especially with RTV boosting)  
• Skin rash  
• Increase in serum creatinine (with COBI) |
| **Evotaz** | Evotaz:  
- (ATV 300 mg plus COBI 150 mg) tablet | Evotaz:  
- 1 tablet once daily  
- Take with food.  
With TDF:  
- Not recommended for patients with baseline CrCl <70 mL/min (see Appendix B, Table 8 for the equation for calculating CrCl). | ATV: as above  
COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor | |

*Note: Generic is available for capsule formulations.*

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## Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 6)

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<thead>
<tr>
<th>Generic Name (Abbreviation) (Trade Name)</th>
<th>Formulations</th>
<th>Dosing Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir (DRV) Prezista</td>
<td>Prezista: • 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension</td>
<td>In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations: • (DRV 800 mg plus RTV 100 mg) once daily In ARV-Experienced Patients with One or More DRV Resistance Mutations: • (DRV 600 mg plus RTV 100 mg) BID Unboosted DRV is not recommended. Take with food.</td>
<td>CYP3A4 inhibitor and substrate; CYP2C9 inducer</td>
<td>15 hours (when combined with RTV)</td>
<td>• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation</td>
</tr>
<tr>
<td>(DRV/c) Prezcobix</td>
<td>Prezcobix: • (DRV 800 mg plus COBI 150 mg) tablet</td>
<td>Prezcobix: • 1 tablet once daily • Take with food. Not recommended for patients with 1 or more DRV resistance-associated mutations. With TDF: • Not recommended for patients with baseline CrCl &lt;70 mL/min (see Appendix B, Table 8 for the equation for calculating CrCl).</td>
<td>DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor</td>
<td>7 hours (when combined with COBI)</td>
<td>• Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)</td>
</tr>
<tr>
<td>(DRV/cTAF/FTC) Symtuza</td>
<td>Symtuza: • (DRV 800 mg plus COBI 150 mg plus TAF 10 mg plus FTC 200 mg) tablet</td>
<td>Symtuza: • 1 tablet once daily with food Not recommended for patients with 1 or more DRV resistance-associated mutations. Not recommended for patients with CrCl &lt;30 mL/min. Not recommended in patients with severe hepatic impairment.</td>
<td>DRV: CYP3A4 inhibitor and substrate; CYP2C9 inducer COBI: CYP3A inhibitor and substrate; CYP2D6 inhibitor</td>
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</table>
### Appendix B, Table 3. Characteristics of Protease Inhibitors  *(Last updated October 25, 2018; last reviewed October 25, 2018)*  (page 3 of 6)

<table>
<thead>
<tr>
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<th>Serum Half-Life</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| *Fosamprenavir (FPV, a prodrug of APV)* | **Lexiva** | • 700 mg tablet  
• 50 mg/mL oral suspension | In ARV-Naive Patients:  
• FPV 1400 mg BID, or  
• (FPV 1400 mg plus RTV 100–200 mg) once daily, or  
• (FPV 700 mg plus RTV 100 mg) BID  
In PI-Experienced Patients (Once-Daily Dosing Not Recommended):  
• (FPV 700 mg plus RTV 100 mg) BID  
With EFV:  
• (FPV 700 mg plus RTV 100 mg) BID, or  
• (FPV 1400 mg plus RTV 300 mg) once daily  
*Tablet:*  
• Without RTV tablet: Take without regard to meals.  
• With RTV tablet: Take with meals.  
*Oral Suspension:*  
• Take without food. | APV is a CYP3A4 substrate, inhibitor, and inducer.  
Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8). | 7.7 hours (APV) | • Skin rash (reported in 12% to 19% of patients on FPV): FPV has a sulfonamide moiety.  
• Diarrhea, nausea, vomiting  
• Headache  
• Hyperlipidemia  
• Serum transaminase elevation  
• Hyperglycemia  
• Fat maldistribution  
• Possible increase in the frequency of bleeding episodes in patients with hemophilia  
• Nephrolithiasis |
| *Indinavir (IDV)* | **Crixivan** | • 200 and 400 mg capsules  
• 200 mg every 8 hours  
• Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal.  
With RTV:  
• (IDV 800 mg plus RTV 100–200 mg) BID  
• Take without regard to meals.  
Drink at least 48 oz of water daily. | CYP3A4 inhibitor and substrate  
Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 8). | 1.5–2 hours | • Nephrolithiasis  
• GI intolerance, nausea  
• Hepatitis  
• Indirect hyperbilirubinemia  
• Hyperlipidemia  
• Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia  
• Hyperglycemia  
• Fat maldistribution  
• Possible increase in the frequency of bleeding episodes in patients with hemophilia |
### Appendix B, Table 3. Characteristics of Protease Inhibitors *(Last updated October 25, 2018; last reviewed October 25, 2018)*  
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<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
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<th>Dosing Recommendations*</th>
<th>Elimination/Metabolic Pathway</th>
<th>Serum Half-Life</th>
<th>Adverse Events*</th>
</tr>
</thead>
</table>
| **Lopinavir/Ritonavir** (LPV/r) **Kaletra** | Kaletra:  
- Tablets: (LPV 200 mg plus RTV 50 mg), or  
- (LPV 100 mg plus RTV 25 mg)  
Oral Solution:  
- Each 5 mL contains (LPV 400 mg plus RTV 100 mg).  
- Oral solution contains 42% alcohol. | Kaletra:  
- (LPV 400 mg plus RTV 100 mg) BID, or  
- (LPV 800 mg plus RTV 200 mg) once daily  
Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. | CYP3A4 inhibitor and substrate | 5–6 hours | GI intolerance, nausea, vomiting, diarrhea  
- Pancreatitis  
- Asthenia  
- Hyperlipidemia (especially hypertriglyceridemia)  
- Serum transaminase elevation  
- Hyperglycemia  
- Insulin resistance/diabetes mellitus  
- Fat maldistribution  
- Possible increase in the frequency of bleeding episodes in patients with hemophilia  
- PR interval prolongation  
- QT interval prolongation and torsades de pointes have been reported; however, causality could not be established. |

| **Nelfinavir** (NFV) **Viracept** | Viracept:  
- 250 and 625 mg tablets | Viracept:  
- NFV 1250 mg BID, or  
- NFV 750 mg TID  
Dissolve tablets in a small amount of water, mix admixture well, and consume immediately.  
Take with food. | CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor | 3.5–5 hours | Diarrhea  
- Hyperlipidemia  
- Hyperglycemia  
- Fat maldistribution  
- Possible increase in the frequency of bleeding episodes in patients with hemophilia  
- Serum transaminase elevation |
### Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 6)

<table>
<thead>
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<th>Serum Half-Life</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| **Ritonavir** (RTV)         | **Norvir** | Norvir:      | As PK Booster (or Enhancer) for Other PIs: | CYP3A4 > 2D6 substrate; potent 3A4, 2D6 inhibitor; inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19 | 3–5 hours | • GI intolerance, nausea, vomiting, diarrhea  
  • Paresthesia (circumoral and extremities)  
  • Hyperlipidemia (especially hypertriglyceridemia)  
  • Hepatitis  
  • Asthenia  
  • Taste perversion  
  • Hyperglycemia  
  • Fat maldistribution  
  • Possible increase in the frequency of bleeding episodes in patients with hemophilia |
|                             |            | • 100 mg tablet  
  • 100 mg soft gel capsule  
  • 80 mg/mL oral solution  
  • 100 mg single packet oral powder  
  Oral solution contains 43% alcohol. | Tablet:  
  • Take with food.  
  Capsule and Oral Solution:  
  • To improve tolerability, take with food if possible. | | |
| **Saquinavir** (SQV)        | **Invirase** | Invirase:    | **Invirase**:  
  (SQV 1000 mg plus RTV 100 mg) BID  
  Unboosted SQV is not recommended.  
  Take with meals or within 2 hours after a meal. | CYP3A4 substrate | 1–2 hours | • GI intolerance, nausea, and diarrhea  
  • Headache  
  • Serum transaminase elevation  
  • Hyperlipidemia  
  • Hyperglycemia  
  • Fat maldistribution  
  • Possible increase in the frequency of bleeding episodes in patients with hemophilia  
  • PR interval prolongation  
  • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV. |
### Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 6)

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<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>Tipranavir (TPV) Aptivus</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Aptivus:</td>
<td>• 250 mg capsule</td>
<td>CYP3A4 inducer and substrate</td>
<td>6 hours</td>
<td>• Hepatotoxicity: clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 100 mg/mL oral solution</td>
<td>CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer</td>
<td>after single dose of TPV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aptivus:</td>
<td>• (TPV 500 mg plus RTV 200 mg)</td>
<td>Net effect of combining TPV and RTV is a CYP3A4 and 2D6 inhibitor</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>BID</td>
<td></td>
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<tr>
<td></td>
<td>With RTV Tablets:</td>
<td>Take with meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>With RTV Capsules or Solution:</td>
<td>Take without regard to meals.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 8.

<sup>b</sup> Also see Table 15.

**Key to Acronyms:** APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase.
### Appendix B, Table 4. Characteristics of Integrase Inhibitors

*(Last updated October 25, 2018; last reviewed October 25, 2018)*

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulations</th>
<th>Dosing Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Elimination/Metabolic Pathways</th>
<th>Serum Half-Life</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bictegravir</strong> (BIC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note</strong>: BIC is only available as a component of an FDC. (BIC/TAF/FTC)</td>
<td>Biktarvy: (BIC 50 mg plus TAF 25 mg plus FTC 200 mg) tablet</td>
<td>Biktarvy: 1 tablet once daily</td>
<td>BIC: CYP3A4 substrate&lt;br&gt;UGT1A1 mediated glucuronidation</td>
<td>~17 hours</td>
<td>Diarrhea&lt;br&gt;Nausea&lt;br&gt;Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dolutegravir</strong> (DTG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tivicay</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Tivicay: 50 mg tablet</td>
<td>In ARV-Naive or ARV-Experienced, INSTI-Naive Patients: 50 mg once daily&lt;br&gt;In ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered with EFV, FPV/r, TPV/r, or Rifampin: 50 mg BID&lt;br&gt;INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance: 50 mg BID Take without regard to meals.</td>
<td>UGT1A1 mediated glucuronidation&lt;br&gt;Minor contribution from CYP3A4</td>
<td>~14 hours</td>
<td>Insomnia&lt;br&gt;Headache&lt;br&gt;Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)&lt;br&gt;Hepatotoxicity&lt;br&gt;Preliminary data suggest increased rate of neural tube defects in infants born to mothers who were taking DTG at the time of conception.&lt;br&gt;HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported.</td>
</tr>
<tr>
<td>(DTG/ABC/3TC) <strong>Triumeq</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triumeq: (DTG 50 mg plus ABC 600 mg plus 3TC 300 mg) tablet</td>
<td>Triumeq: 1 tablet once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(DTG/RPV) <strong>Juluca</strong></td>
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</tr>
<tr>
<td></td>
<td>Juluca: (DTG 50 mg plus RPV 25 mg) tablet</td>
<td>Juluca: 1 tablet once daily with a meal</td>
<td></td>
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</tr>
</tbody>
</table>
## Characteristics of Integrase Inhibitors

### Appendix B, Table 4

Last updated October 25, 2018; last reviewed October 25, 2018

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulations</th>
<th>Dosing Recommendations*</th>
<th>Elimination/Metabolic Pathways</th>
<th>Serum Half-Life</th>
<th>Adverse Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elvitegravir (EVG)</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>• Nausea</td>
</tr>
<tr>
<td><strong>Note:</strong> EVG is only available as a component of an FDC.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td><strong>(EVG/c/FTC/TAF) Genvoya</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)</td>
</tr>
<tr>
<td><strong>(EVG/c/FTC/TDF) Stribild</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raltegravir (RAL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isentress/Isentress HD</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Appendix B, Table 5. Characteristics of the Fusion Inhibitor  (Last updated January 29, 2008; last reviewed October 25, 2018)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Serum Half-Life</th>
<th>Elimination</th>
<th>Adverse Events&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>Fuzeon</td>
<td>Fuzeon:</td>
<td>• Injectable; supplied as lyophilized powder</td>
<td>3.8 hours Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool</td>
<td>• Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) occur in almost 100% of patients</td>
<td>• Increased incidence of bacterial pneumonia • HSR (&lt;1% of patients). Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. <strong>Rechallenge is not recommended.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. • Refer to prescribing information for storage instruction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Also see Table 15.

**Key to Abbreviations:** BID = twice daily; HSR = hypersensitivity reaction; T-20 = enfuvirtide

### Appendix B, Table 6. Characteristics of CCR5 Antagonist  (Last updated March 27, 2012; last reviewed October 25, 2018)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Serum Half-Life</th>
<th>Elimination/Metabolic Pathway</th>
<th>Adverse Events&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc (MVC)</td>
<td>Selzentry</td>
<td>Selzentry:</td>
<td>• 150 and 300 mg tablets</td>
<td>14–18 hours</td>
<td>CYP3A4 substrate</td>
<td>• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions • Orthostatic hypotension, especially in patients with severe renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Fuzeon</td>
<td>Fuzeon:</td>
<td>• 90 mg (1 mL) subcutaneously BID</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For dosage adjustment in hepatic insufficiency, see Appendix B, Table 8.

<sup>b</sup> Also see Table 15.

**Key to Acronyms:** BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir
### Appendix B, Table 7. Characteristics of CD4 Post-Attachment Inhibitor (Last updated October 25, 2018; last reviewed October 25, 2018)

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Serum Half-Life</th>
<th>Elimination/ Metabolic Pathway</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibalizumab (IBA) Trogarzo</td>
<td>Trogarzo:</td>
<td>Trogarzo:</td>
<td>~64 hours</td>
<td>Not well defined.</td>
<td>• Diarrhea</td>
</tr>
</tbody>
</table>
|                             | • Single-dose 2 mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab | • Administer a single loading dose of IBA 2000 mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800 mg IV infusion over 15 minutes every 2 weeks.  
  • See prescribing information for additional instruction in preparation, storage, administration, and monitoring. | | | • Dizziness |
|                            |             |                        |                 |                               | • Nausea      |
|                            |             |                        |                 |                               | • Rash        |

**Key to Acronyms:** IBA = ibalizumab; IV = intravenous
**Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency** (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 7)

See the reference section at the end of this table for CrCl calculation formulas and criteria for Child-Pugh classification.

<table>
<thead>
<tr>
<th>ARVs</th>
<th>Generic Name (Abbreviation)</th>
<th>Usual Daily Dosea</th>
<th>Dosing in Patients with Renal Insufficiencyb</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stribild should not be initiated in patients with CrCl &lt;70 mL/min. The following FDCs are not recommended in patients with CrCl &lt;50 mL/min: Atripla, Combivir, Complera, Delstrigo, Epzicom, Trumeq, or Trizivir. Biktarvy, Descovy, Genvoya, Odefsey, Symtuza, and Truvada are not recommended in patients with CrCl &lt;30 mL/min.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abacavir</strong> (ABC)</td>
<td>Ziagen</td>
<td>• 300 mg PO BID, or • 600 mg PO once daily</td>
<td>No dose adjustment necessary.</td>
<td>Child-Pugh Class A: • 200 mg PO BID (use oral solution) Child-Pugh Class B or C: • Contraindicated</td>
</tr>
<tr>
<td><strong>Didanosine EC</strong> (ddI)</td>
<td>Videx EC</td>
<td>Body Weight ≥60 kg: • 400 mg PO once daily Body Weight &lt;60 kg: • 250 mg PO once daily</td>
<td>Once-Daily Dose by Body Weight</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Didanosine Oral Solution</strong> (ddI)</td>
<td>Videx</td>
<td>Body Weight ≥60 kg: • 200 mg PO BID, or • 400 mg PO once daily Body Weight &lt;60 kg: • 250 mg PO once daily, or • 125 mg PO BID</td>
<td>Once-Daily Dose by Body Weight</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Emtricitabine</strong> (FTC)</td>
<td>Emtriva</td>
<td>• 200 mg oral capsule once daily, or • 240 mg (24 mL) oral solution once daily</td>
<td>Dose</td>
<td>No dose recommendation.</td>
</tr>
<tr>
<td><strong>Lamivudine</strong> (3TC)</td>
<td>Epivir</td>
<td>• 300 mg PO once daily, or • 150 mg PO BID</td>
<td></td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td><strong>Stavudine</strong> (d4T)</td>
<td>Zerit</td>
<td>Body Weight ≥60 kg: • 40 mg PO BID Body Weight &lt;60 kg: • 30 mg PO BID</td>
<td>Dose</td>
<td>No dose recommendation</td>
</tr>
</tbody>
</table>

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

Downloaded from https://aidsinfo.nih.gov/guidelines on 1/1/2019
### ARVs

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Usual Daily Dose</th>
<th>Dosing in Patients with Renal Insufficiency</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs, continued</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Tenofovir Alafenamide/Emtricitabine (TAF/FTC) Descovy | • TAF for HIV treatment is only available as a component of FDCs (i.e., Descovy, Genvoya, Odefsey, Biktarvy, and Symtuza).  
• TAF 10 mg PO daily with EVG/c (Genvoya) or DRV/c (Symtuza)  
• TAF 25 mg PO daily in other FDCs | CrCl (ml/min) | Dose | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| Tenofovir Disoproxil Fumarate (TDF) Viread | • 300 mg PO once daily | CrCl (mL/min) | Dose | No dose adjustment necessary. |
| Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) Truvada | • 1 tablet PO once daily | CrCl (mL/min) | Dose | No dose recommendation. |
| Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) Cimduo | • 1 tablet PO once daily | CrCl (mL/min) | Dose | No dose recommendation. |
| Zidovudine (ZDV) Retrovir | • 300 mg PO BID | CrCl (mL/min) | Dose | No dose recommendation. |
| **NNRTIs**                  |            |                  |                                             |                                            |
| Doravirine (DOR) Pifeltro    | • 1 tablet PO once daily | No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in ESRD or HD. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• Not studied |
| Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine (DOR/TDF/3TC) Delstrigo | • 1 tablet PO once daily | No recommended if CrCl <50 mL/min. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• Not studied |
| Efavirenz (EFV) Sustiva      | • 600 mg PO once daily, on an empty stomach, preferably at bedtime | No dose adjustment necessary. | No dose recommendation; use with caution in patients with hepatic impairment. |
| Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine (EFV/TDF/FTC) Atripla | • 1 tablet once daily on an empty stomach, preferably at bedtime | Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust TDF and FTC doses according to CrCl level. | No dose recommendation; use with caution in patients with hepatic impairment. |
### Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

(Last updated October 25, 2018; last reviewed October 25, 2018)  
(page 3 of 7)

<table>
<thead>
<tr>
<th>ARVs Generic Name (Abbreviation) Trade Name</th>
<th>Usual Daily Dose$^a$</th>
<th>Dosing in Patients with Renal Insufficiency$^b$</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz 600 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) Symfi</strong></td>
<td>• 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td>Not recommended if CrCl &lt;50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.</td>
<td>Not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.</td>
</tr>
<tr>
<td><strong>Efavirenz 400 mg/ Tenofovir Disoproxil Fumarate/Lamivudine (EFV/TDF/3TC) Symfi Lo</strong></td>
<td>• 1 tablet once daily on an empty stomach, preferably at bedtime</td>
<td>Not recommended if CrCl &lt;50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.</td>
<td>Not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.</td>
</tr>
</tbody>
</table>
| **Etravirine (ETR) Intelence** | • 200 mg PO BID | No dose adjustment necessary. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| **Nevirapine (NVP) Viramune or Viramune XR** | • 200 mg PO BID, or  
• 400 mg PO once daily (using Viramune XR formulation) | No dose adjustment for patients with renal impairment.  
Patients on HD should receive an additional dose of 200 mg following each dialysis treatment. | Child-Pugh Class A:  
• No dose adjustment  
Child-Pugh Class B or C:  
• Contraindicated |
| **Rilpivirine (RPV) Edurant** | • 25 mg PO once daily | No dose adjustment necessary. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| **Rilpivirine/Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) Odefsey** | • 1 tablet PO once daily | Not recommended if CrCl <30 mL/min. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| **Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) Complera** | • 1 tablet PO once daily | Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust TDF and FTC doses according to CrCl level. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| **Rilpivirine/ Dolutegravir (RPV/DTG) Juluca** | • 1 tablet PO once daily/ with food | No dose adjustment necessary.  
In patients with CrCl <30 mL/min, monitor closely for adverse effects. | Child-Pugh Class A or B:  
• No dose adjustment  
Child-Pugh Class C:  
• No dose recommendation |
| **PIs** | | | |
| **Atazanavir (ATV) Reyataz** | • 400 mg PO once daily, or  
• (ATV 300 mg plus RTV 100 mg) PO once daily | No dose adjustment for patients with renal dysfunction who do not require HD.  
In ARV-Naive Patients on HD:  
• (ATV 300 mg plus RTV 100 mg) once daily  
In ARV-Experienced Patients on HD:  
• ATV or ATV/r not recommended  
RTV boosting is not recommended in patients with hepatic impairment. | Child-Pugh Class B:  
• 300 mg once daily (unboosted) for ARV-naive patients only  
Child-Pugh Class C:  
• Not recommended  
RTV boosting is not recommended in patients with hepatic impairment. |
<table>
<thead>
<tr>
<th>ARVs Generic Name (Abbreviation) Trade Name</th>
<th>Usual Daily Dose</th>
<th>Dosing in Patients with Renal Insufficiency</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atazanavir/Cobicistat (ATV/c) Evotaz</strong></td>
<td>• 1 tablet PO once daily</td>
<td>If Used with TDF: • Not recommended if CrCl &lt;70 mL/min</td>
<td>Not recommended in patients with hepatic impairment.</td>
</tr>
<tr>
<td><strong>Darunavir (DRV) Prezista</strong></td>
<td>In ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations: (DRV 800 mg plus RTV 100 mg) PO once daily with food, In ARV-Experienced Patients with at Least 1 DRV Resistance Mutation: (DRV 600 mg plus RTV 100 mg) PO BID</td>
<td>No dose adjustment necessary.</td>
<td>In Patients with Mild-to-Moderate Hepatic Impairment: • No dose adjustment In Patients with Severe Hepatic Impairment: • Not recommended</td>
</tr>
<tr>
<td><strong>Darunavir/Cobicistat (DRV/c) Prezcobix</strong></td>
<td>• 1 tablet PO once daily</td>
<td>If Used with TDF: • Not recommended if CrCl &lt;70 mL/min</td>
<td>Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • Not recommended</td>
</tr>
<tr>
<td><strong>Darunavir/Cobicistat/Tenofovir Alafenamide/ Emtricitabine (DRV/c/TAF/FTC) Symtuza</strong></td>
<td>• 1 tablet PO once daily</td>
<td>Not recommended if CrCl &lt;30 mL/min.</td>
<td>Not recommended for patients with severe hepatic impairment.</td>
</tr>
<tr>
<td><strong>Fosamprenavir (FPV) Lexiva</strong></td>
<td>• 1400 mg PO BID, or (FPV 1400 mg plus RTV 100–200 mg) PO once daily, or (FPV 700 mg plus RTV 100 mg) PO BID</td>
<td>No dose adjustment necessary.</td>
<td>In PI-Naive Patients Only Child-Pugh Score 5–9: • 700 mg BID Child-Pugh Score 10–15: • 350 mg BID In PI-Naive or PI-Experienced Patients Child-Pugh Score 5–6: • (FPV 700 mg BID plus RTV 100 mg) once daily Child-Pugh Score 7–9: • (FPV 450 mg BID plus RTV 100 mg) once daily Child-Pugh Score 10–15: • (FPV 300 mg BID plus RTV 100 mg) once daily</td>
</tr>
</tbody>
</table>
### ARVs, continued

<table>
<thead>
<tr>
<th>ARVs</th>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Usual Daily Dosea</th>
<th>Dosing in Patients with Renal Insufficiencyb</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>• 800 mg PO q8h</td>
<td>No dose adjustment necessary.</td>
<td>In Patients with Mild-to-Moderate Hepatic Insufficiency Due to Cirrhosis: • 600 mg q8h</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (LPV/r)</td>
<td>Kaletra</td>
<td>• (LPV 400 mg plus RTV 100 mg) PO BID, or • (LPV 800 mg plus RTV 200 mg) PO once daily</td>
<td>Avoid once-daily dosing in patients on HD.</td>
<td>No dose recommendation; use with caution in patients with hepatic impairment.</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
<td>• 1250 mg PO BID</td>
<td>No dose adjustment necessary.</td>
<td>In Patients with Mild Hepatic Impairment: • No dose adjustment</td>
<td>In Patients with Moderate-to-Severe Hepatic Impairment: • Not recommended</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
<td>As a PI-Boosting Agent: • 100–400 mg per day</td>
<td>No dose adjustment necessary.</td>
<td>Refer to recommendations for the primary PI.</td>
<td></td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>Invirase</td>
<td>• (SQV 1000 mg plus RTV 100 mg) PO BID</td>
<td>No dose adjustment necessary.</td>
<td>In Patients with Mild-to-Moderate Hepatic Impairment: • Use with caution</td>
<td>In Patients with Severe Hepatic Impairment: • Contraindicated</td>
</tr>
<tr>
<td>Tipranavir (TPV)</td>
<td>Aptivus</td>
<td>• (TPV 500 mg plus RTV 200 mg) PO BID</td>
<td>No dose adjustment necessary.</td>
<td>Child-Pugh Class A: • Use with caution</td>
<td>Child-Pugh Class B or C: • Contraindicated</td>
</tr>
<tr>
<td><strong>INSTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bictegravir/Tenofovir Alafenamide/Emtricitabine (BIC/TAF/FTC)</td>
<td>Biktarvy</td>
<td>• 1 tablet once daily</td>
<td>Not recommended for use in patients with CrCl &lt;30 mL/min.</td>
<td>Child-Pugh Class C: • Not recommended</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td>Tivicay</td>
<td>• 50 mg once daily, or • 50 mg BID</td>
<td>No dose adjustment necessary.</td>
<td>Child-Pugh Class A or B: • No dose adjustment</td>
<td>Child-Pugh Class C: • Not recommended</td>
</tr>
</tbody>
</table>
## Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 7)

<table>
<thead>
<tr>
<th>ARVs Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Usual Daily Dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing in Patients with Renal Insufficiency&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INSTIs, continued</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dolutegravir/Abacavir/Lamivudine (DTG/ABC/3TC)</strong></td>
<td><strong>Triumeq</strong></td>
<td>• 1 tablet once daily</td>
<td>Not recommended if CrCl &lt;50 mL/min. Instead, use the individual drugs and adjust 3TC dose according to CrCl.</td>
<td>Child-Pugh Class A: • Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the fixed-dose combination in these patients. Child-Pugh Class B or C: • Contraindicated, due to the ABC component</td>
</tr>
<tr>
<td><strong>Dolutegravir/Rilpivirine (DTG/RPV)</strong></td>
<td><strong>Juluca</strong></td>
<td>• 1 tablet PO once daily with food</td>
<td>No dose adjustment necessary. In patients with CrCl &lt;30 mL/min, monitor closely for adverse effects.</td>
<td>Child-Pugh Class A or B: • No dose adjustment Child-Pugh Class C: • No dose recommendation</td>
</tr>
<tr>
<td><strong>Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine (EVG/c/TAF/FTC)</strong></td>
<td><strong>Genvoya</strong></td>
<td>• 1 tablet once daily</td>
<td>Not recommended for use in patients with CrCl &lt;30 mL/min.</td>
<td>In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • Not recommended</td>
</tr>
<tr>
<td><strong>Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine (EVG/c/TDF/FTC)</strong></td>
<td><strong>Stribild</strong></td>
<td>• 1 tablet once daily</td>
<td>EVG/c/TDF/FTC should not be initiated in patients with CrCl &lt;70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to &lt;50 mL/min while patient is on therapy.</td>
<td>In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • Not recommended</td>
</tr>
<tr>
<td><strong>Raltegravir (RAL)</strong></td>
<td><strong>Isentress</strong> <strong>Isentress HD</strong></td>
<td>• 400 mg BID (using Isentress formulation), or • 1200 mg once daily (use Isentress HD formulation only)</td>
<td>No dose adjustment necessary.</td>
<td>In Patients with Mild-to-Moderate Hepatic Insufficiency: • No dose adjustment necessary In Patients with Severe Hepatic Insufficiency: • No recommendation</td>
</tr>
<tr>
<td><strong>Fusion Inhibitor</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Enfuvirtide (T-20)</strong></td>
<td><strong>Fuzeon</strong></td>
<td>• 90 mg subcutaneous BID</td>
<td>No dose adjustment necessary.</td>
<td>No dose adjustment necessary.</td>
</tr>
</tbody>
</table>
## Appendix B, Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency  
**Last updated October 25, 2018; last reviewed October 25, 2018**  
(page 7 of 7)

<table>
<thead>
<tr>
<th>ARVs Generic Name (Abbreviation)</th>
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<th>Dosing in Patients with Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCR5 Antagonist</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Maraviroc (MVC)                 | Seizentry  | • The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information. | In Patients with CrCl $<30$ mL/min or Patients Who Are on HD Without Potent CYP3A Inhibitors or Inducers:  
  • 300 mg BID; reduce to 150 mg BID if postural hypotension occurs  
With Potent CYP3A Inducers or Inhibitors:  
  • Not recommended | No dose recommendations. MVC concentrations will likely be increased in patients with hepatic impairment. |

| **CD4 Post-Attachment Inhibitor** | | | |
| Ibalizumab (IBA) | Trogarzo | • Loading dose of 2000 mg IV, followed by a maintenance dose of 800 mg IV every 2 weeks | No dose adjustment recommended. | No recommendation. |

<sup>a</sup> Refer to Appendix B, Tables 1–7 for additional dosing information.

<sup>b</sup> Including patients who are on CAPD and HD.

<sup>c</sup> On dialysis days, take dose after HD session.

**Key to Acronyms:**  
3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AZT = zidovudine; BIC = bictegravir; BID = twice daily; CAPD = chronic ambulatory peritoneal dialysis; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddl = didanosine; DLV = delavirdine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; DOR = doravirine; EC = enteric coated; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IBA = ibalizumab; IDV = indinavir; INSTI = integrase strand transfer inhibitor; IV=intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nefavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; q(n)d = every (n) days; q(n)h = every (n) hours; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZDV = zidovudine
<table>
<thead>
<tr>
<th>Component</th>
<th>Points Scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5 g/dL</td>
</tr>
<tr>
<td>Total bilirubin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;2 mg/dL (&lt;34 μmol/L)</td>
</tr>
<tr>
<td>Modified total bilirubin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;4 mg/dL</td>
</tr>
<tr>
<td>Prothrombin time (seconds prolonged) or International normalized ratio (INR)</td>
<td>&lt;4</td>
</tr>
<tr>
<td></td>
<td>2.8–3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>4–7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt;4 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt;2 mg/dL (&gt;50 μmol/L)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 mg/dL (&gt;50 μmol/L)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Encephalopathy Grades

- **Grade 1**: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
- **Grade 2**: Drowsiness, disorientation, asterixis
- **Grade 3**: Somnolent but rousable, marked confusion, incoherent speech, incontinence, hyperventilation
- **Grade 4**: Coma, decerebrate posturing, flaccidity

<sup>b</sup> Modified total bilirubin used for patients who have Gilbert’s syndrome or who are taking indinavir or atazanavir

### Child-Pugh Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Total Child-Pugh Score&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>5–6 points</td>
</tr>
<tr>
<td>Class B</td>
<td>7–9 points</td>
</tr>
<tr>
<td>Class C</td>
<td>&gt;9 points</td>
</tr>
</tbody>
</table>

<sup>a</sup> Sum of points for each component of the Child-Pugh Score