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

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

How to Cite the Adult and Adolescent Guidelines:

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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 AIDS*info* Web site (http://aidsinfo.nih.gov).

What's New in the Guidelines? (Last updated July 10, 2019; last reviewed July 10, 2019)

This guideline update focuses on three sections: (1) Transgender People with HIV, a new section in the guidelines; (2) Substance Use Disorders and HIV, a completely rewritten section that was formerly called HIV and People Who Use Illicit Drugs; and (3) HIV-2 Infection. Revisions to other sections of the guidelines are expected to be released in late 2019.

Transgender People with HIV

Transgender and nonbinary people bear a disproportionate burden of HIV. According to the most recent estimate, 14% of transgender women have HIV and 2% of transgender men have HIV. To address the specific HIV care needs of these individuals, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) has created a new section of the guidelines. This section focuses on:

- The importance of providing HIV care services within a gender-affirmative care model to reduce potential barriers to antiretroviral therapy (ART) adherence and maximize the likelihood of achieving sustained viral suppression;
- The role of gender-affirming hormonal therapy and the potential interactions between these drugs and certain antiretroviral (ARV) drugs; *and*
- Potential health impacts of gender-affirming hormonal therapy on transgender persons with HIV.

Substance Use Disorders and HIV

The Panel notes that substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care.

This newly expanded section now includes information on the following substances: alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The discussions focus on the potential health consequences of each substance for persons with HIV, the role of providers in managing patients with SUDs, the impact of SUDs on the HIV continuum of care and ART, and treatment options for these SUDs.

HIV-2 Infection

This section has been revised to focus on when to start ART and which ARV regimens to use in persons with HIV-2 monoinfection or HIV-1/HIV-2 coinfection. The key revisions are as follows:

- Previously, the Panel recommended starting ART in persons with HIV-2 before clinical progression. Existing data on the treatment of HIV-2, and extrapolation from data on the treatment of HIV-1, suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others **(AIII)**.
- No randomized controlled clinical trials have determined which ARV regimens are the most effective for treating HIV-2. However, since the last revision, two single-arm clinical trials have shown favorable outcomes in patients receiving integrase strand transfer inhibitor (INSTI)-based regimens **(AII)**. On the basis of these study results, the Panel recommends using an INSTI-based regimen as an initial ART regimen for treatment-naive patients with HIV-2. A regimen that includes a boosted protease inhibitor that is active against HIV-2 (darunavir or lopinavir) can be used as an alternative **(BII)**.

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

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition. In addition, ART is highly effective at preventing HIV transmission.[1] However, only 55% of people with HIV in the United States have suppressed viral loads,[2] mostly resulting from undiagnosed HIV infection and failure to link or retain diagnosed patients in care.

The Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide HIV care practitioners with recommendations based on current knowledge of antiretroviral drugs (ARVs) used to treat adults and adolescents with HIV in the United States. The Panel reviews new evidence and updates recommendations when needed. These guidelines include recommendations on baseline laboratory evaluations, treatment goals, benefits of ART and considerations when initiating therapy, choice of the initial regimen for ART-naive patients, ARV drugs or combinations to avoid, management of treatment failure, management of adverse effects and drug interactions, and special ART-related considerations in specific patient populations. This Panel works closely with the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children to provide recommendations for adolescents at different stages of growth and development. Recommendations for ART regimens in these guidelines are most appropriate for postpubertal adolescents (i.e., sexual maturity rating [SMR] IV and V). Clinicians should follow recommendations in the Pediatric Guidelines when initiating ART in adolescents at SMR III or lower.[3] For recommendations related to pre- (PrEP) and post- (PEP) HIV exposure prophylaxis for people who do not have HIV, clinicians should consult recommendations from the Centers for Disease Control and Prevention (CDC).[4]

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

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

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

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

Basis for Recommendations

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

Table 2. Rating Scheme for Recommendations

Strength of Recommendation[i]	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in patients with HIV are better when care is delivered by clinicians with HIV expertise (e.g., care for a larger panel of patients),[5-9] 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.

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

Every patient with HIV entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the diagnosis of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and to initiate care as recommended in HIV primary care guidelines[1] and guidelines for prevention and treatment of HIV-associated opportunistic infections.[2] The initial evaluation also should include discussion on the benefits of antiretroviral therapy (ART) for the patient's health and to prevent HIV transmission. Baseline information then can be used to define management goals and plans. In the case of previously treated patients who present for an initial evaluation with a new health care provider, it is critical to obtain a complete antiretroviral (ARV) history (including drug resistance testing results, if available), preferably through the review of past medical records. Newly diagnosed patients should also be asked about any prior use of ARV agents for prevention of HIV infection.

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

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

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

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

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

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Laboratory Testing

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

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

Two surrogate markers are routinely used to monitor patients with HIV: CD4 T lymphocyte (CD4) cell count to assess immune function, and plasma HIV RNA (viral load) to assess level of HIV viremia. Resistance testing should be used to guide selection of an ARV regimen. A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist. HLA-B*5701 testing should be performed before initiation of abacavir (ABC). Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART and, if indicated, periodically after ART initiation, as treatment of these coinfections may affect the choice of ART. The rationale for and utility of some of these laboratory tests are discussed in the corresponding sections of the Guidelines.

Table 3. Laboratory Testing Schedule for Monitoring Patients with HIV Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 3)

Laboratory Test	Timepoint or Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√ During first 2 years of ART, or if viremia develops while patient is on ART, or if CD4 count is <300 cells/mm^3		√ <u>After 2 Years on ART with Consistently Suppressed Viral Load</u>: *CD4 Count 300–500 cells/mm^3:* • Every 12 months *CD4 Count >500 cells/mm^3:* • CD4 monitoring is optional.	√	√	√ Every 3–6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional.
Resistance Testing	√	√[f]					√	√	√[f]
HLA-B*5701 Testing		√ If considering ABC							

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

Laboratory Test	Timepoint or Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist, or for patients experiencing virologic failure on a CCR5 antagonist-based regimen	√	
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)[g,h,i]	√	√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]				√ May repeat if patient is nonimmune and does not have chronic HBV infection[h]		√ Including prior to starting HCV DAA (see HCV/HIV Coinfection)	
Hepatitis C Screening (HCV antibody or, if indicated, HCV RNA)[j]	√					√ Repeat HCV screening for at-risk patients[k]		√	
Basic Chemistry[l,m]	√	√	√	√				√	√ Every 6–12 months
ALT, AST, Total Bilirubin	√	√	√	√				√	√ Every 6–12 months
CBC with Differential	√	√	√ If on ZDV	√ If on ZDV or if CD4 testing is done	√			√	√ Every 3–6 months

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

Laboratory Test	Timepoint or Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Fasting Lipid Profile[n]	√	√			√ If abnormal at last measurement	√ If normal at last measurement		√	√ If normal at baseline, annually
Fasting Glucose or Hemoglobin A1C	√	√		√ If abnormal at last measurement		√ If normal at last measurement		√	√ If normal at baseline, annually
Urinalysis[m,o]	√	√			√ If on TAF or TDF[l]	√		√	
Pregnancy Test[p]	√	√						√	

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

[b] If ART initiation occurs soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] ART is indicated for all individuals with HIV and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

[d] If HIV RNA is detectable at 2 to 8 weeks, repeat testing every 4 to 8 weeks until viral load is suppressed to <200 copies/mL. Thereafter, repeat testing every 3 to 6 months.

[e] In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

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

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

[h] If HBsAg, HBsAb, and HBcAb test results are negative, hepatitis B vaccine series should be administered. Refer to the HIV Primary Care Guidelines and the Adult and Adolescent Opportunistic Infections Guidelines for detailed recommendations.[1,2]

[i] Most patients with isolated HBcAb have resolved HBV infection with loss of HBsAb. Consider performing an HBV viral load for confirmation. If the HBV viral load is positive, the patient may be acutely infected (and will usually display other signs of acute hepatitis) or chronically infected. If negative, the patient should be vaccinated. Refer to the HIV Primary Care Guidelines and the Adult

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

[j] The HCV antibody test may not be adequate for screening in the setting of recent HCV infection (defined as acquisition within the past 6 months), or advanced immunodeficiency (CD4 count <100 cells/mm^3). HCV RNA screening is indicated in persons who have been successfully treated for HCV or who spontaneously cleared prior infection. HCV antibody-negative patients with elevated ALT may need HCV RNA testing.

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

[l] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or TDF-containing regimens.[3]

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

[n] Consult the National Lipid Association's recommendations for management of patients with dyslipidemia.[4]

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

[p] This applies to people of childbearing potential.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CD4 = CD4 T lymphocyte; Cl = chloride; DAA = direct-acting antiviral; FTC = emtricitabine; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; K = potassium; Na = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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

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

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.[1] The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy **after** initiation of ART.

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

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

Plasma HIV-1 RNA (Viral Load) Monitoring

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

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-3] Thus, viral load testing is an established surrogate marker for treatment response.[4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 $\log_{10}$ copies/mL change). Optimal viral suppression is defined generally as a viral load persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not predictive of virologic failure.[5] Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One recent study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.[6-9] These guidelines and the AIDS Clinical Trials Group (ACTG) now define virologic failure as a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see Virologic Failure and Suboptimal Immunologic Response).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it

may take longer. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART or modification of therapy because of virologic failure.** Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification **(AIII)**. The purpose of the measurements is to confirm an adequate initial virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII)**.
- **In virologically suppressed patients in whom ART was modified because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy **(AIII)**. The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load should be repeated every 3 to 4 months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable **(AIII)**.
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen (see Drug-Resistance Testing and Virologic Failure and Suboptimal Immunologic Repsonse sections).

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies.[11,12] CD4 counts are highly variable; a significant change (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it is **not routinely recommended (BIII)**.

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all patients at entry into care **(AI)**. It is the key factor in determining the need to initiate OI prophylaxis (see the Adult Opportunistic Infection Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiating Antiretroviral Therapy section of these guidelines). Although most OIs occur in patients with CD4 counts <200 cells/mm^3, some OIs can occur in patients with higher CD4 counts.[14]

Use of CD4 Count for Monitoring Therapeutic Response

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult Opportunistic Infection Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm^3 during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 to 100 cells/mm^3 per year until a steady state level is reached.[15] Patients who initiate therapy with a low CD4 count[16,17] or at an older age[18] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

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

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII)**. This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the guidelines for treatment and prophylaxis of opportunistic infections.[13] In this setting, and in the first 2 years following ART initiation, CD4 count can be monitored at 3- to 6- month intervals **(BII)**.

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 count provides limited information. Frequent testing is unnecessary because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm^3 are rare in patients with viral suppression and CD4 counts >300 cells/mm^3.[19] Similarly, the ARTEMIS trial found that CD4 monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[20] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 and 200 cells/mm^3.[21] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes such as cardiovascular disease, malignancy, and death.[22] An analysis of costs associated with CD4 monitoring in the United States estimated that reducing CD4 monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.[23]

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

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy[24,25] or coinfection with human T-lymphotropic virus type I (HTLV-1)[26] may cause misleadingly elevated CD4 counts. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage.[27] In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

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

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

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

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

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

Panel's Recommendations

For Antiretroviral Therapy-Naive Persons:

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

For Antiretroviral Therapy-Experienced Persons:

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

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

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

Genotypic and Phenotypic Resistance Assays

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

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes; in general, these assays require a plasma viral load of at least 500 to 1,000 copies/mL. Most genotypic assays involve conventional Sanger sequencing of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes of circulating RNA in plasma to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene associated with resistance to the fusion inhibitor enfuvirtide is also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpreting these test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains an updated list of significant resistance-associated mutations in the RT, PR, IN, and envelope genes. The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results.[1] Various additional tools are also available to assist providers in interpreting genotypic test results.[2-5] Clinical trials have demonstrated that consulting with specialists in HIV drug resistance improves virologic outcomes.[6] Clinicians are thus encouraged to consult a specialist to interpret genotypic test results and design optimal new regimens.

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

Phenotypic Assays

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

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpreting phenotypic assay results can be complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) associated with drug failure, although clinically significant fold increase cutoffs have been described for some drugs.[7-11] Again, consulting with a specialist to interpret test results can be helpful.

Limitations of Genotypic and Phenotypic Assays

Limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Drug-resistant viruses that constitute <10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important to note because a wild-type virus often re-emerges as the predominant population in the plasma after discontinuation of drugs that exert selective pressure on drug-resistant populations. As a consequence, the proportion of virus with resistance mutations can decrease to below the 10% to 20% threshold.[12-14] In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus.[15] Therefore, resistance testing is most valuable when performed while a person experiencing virologic failure is still taking ARV drugs or, if that is not possible,

then within 4 weeks after discontinuing therapy **(AII)**. Because resistant viruses may persist longer in the plasma of some patients, resistance testing that is done 4 to 6 weeks after discontinuation of drugs or later may still detect mutations and provide useful information to guide therapy **(CIII)**. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens. Importantly, in addition to considering prior antiretroviral therapy (ART) history, prior genotypic- or phenotypic-resistance test results should be obtained from old records when possible. Because the most current drug-resistance test may not be able to detect resistance mutations that were previously detected, these prior test results are clinically important and should be used when designing a new regimen **(AIII)**.

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

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

Use of Resistance Assays in Determining Initial Treatment

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

Resistance testing can guide therapy selection to optimize virologic response in people with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis. Therefore, resistance testing in these situations is recommended (AII). A genotypic assay is preferred for this purpose **(AIII)**. In these settings, treatment initiation should not be delayed pending resistance testing results if the individual is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see also Acute and Recent HIV [Early] Infection). In the absence of ART, resistant viruses may decline over time to less than the detection limit of standard resistance tests. However, when ART is eventually initiated, even low levels of resistant viruses may still increase the risk of treatment failure.[26-28] Therefore, if ART is deferred, resistance testing should still be performed during early HIV infection **(AIII)**. In this situation, the genotypic resistance test result should be used for regimen selection when the person begins ART. Repeat resistance testing at the start of treatment may also be considered, because a patient may acquire drug-resistant virus (i.e., superinfection) between entry-into-care and the initiation of ART (CIII).[29]

Interpretation of drug-resistance testing before ART initiation in persons with chronic HIV is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.[30-32] Though no prospective trial has directly addressed whether drug-resistance testing before initiation of therapy confers benefit in this population, data from several studies, including one prospective clinical trial, suggest that virologic responses in persons with baseline resistance mutations are suboptimal.[16-19,33-37] In addition, an analysis of early RT and PR genotypic resistance testing in ARV-naive persons suggests that baseline testing in this population is cost effective and should be performed.[38] Therefore, resistance testing in people with chronic infections is recommended at the time of entry into HIV care **(AII)**.

Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred over phenotypic testing because of lower cost, more rapid turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier interpretation of test results **(AIII)**. If therapy is deferred, repeat testing shortly before initiating ART may be considered, because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.[29] Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the RT and PR genes. Although reports of transmission of INSTI-resistant virus are rare, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers should supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs, which may need to be ordered separately **(AIII)**.

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

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are important tools to inform treatment decisions for patients who experience virologic failure while on ART. Several prospective studies have assessed the utility of resistance testing to guide ARV drug selection in patients who experience virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6,39-45] In general, these studies found that changes in therapy based on resistance test results produced better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that the use of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[46] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see also Virologic Failure). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Conventional drug-resistance testing in persons with plasma viral loads <500 copies/mL is not usually recommended, because resistance assays cannot be consistently performed at low HIV RNA levels **(AIII)**.

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of ART is, for certain patients, associated with resistance to only one component of the regimen.[47-49] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

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

When compared with phenotypic testing, genotypic testing costs less to perform and has a faster turnaround time

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

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

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

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

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

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

Use of Resistance Assays in Pregnancy

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

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

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

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

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

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

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Co-Receptor Tropism Assays (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations
• A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**. • Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**. • A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI)**. • A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII)**. • A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) **(BII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

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

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

Phenotypic Assays

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

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the Trofile® assay.[12] This earlier assay failed to routinely detect low levels of CXCR4 utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low levels of such variants at baseline, which were below the assay limit of detection, and these patients exhibited rapid virologic failure after initiation of a CCR5 antagonist.[13] The assay has been improved and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones represent 0.3% or more of the virus population.[14] Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only assay that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the Trofile® assay.

In patients with an undetectable viral load or detectable plasma HIV RNA <1,000 copies/mL, phenotypic co-receptor usage can be determined using proviral DNA obtained from peripheral blood mononuclear cells (e.g., Trofile® DNA, Monogram Sciences); however, the clinical utility of this assay remains to be determined.[15]

Genotypic Assays

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 *env*, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence.[16] When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50% to 75%) for the presence of a CXCR4-utilizing virus. Studies in which V3 genotyping was performed on samples from patients screened for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC.[17-19] An important caveat is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (Trofile®). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. Other studies have also demonstrated relatively high concordance between genotypic- and phenotypic-assessed tropism;[20,21] however, there is variability between different genotypic platforms.[22]

Given these performance characteristics, genotypic tropism assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant;[23] therefore, the Panel preferentially recommends phenotypic testing. Based on accessibility, capacity, logistics, and cost, European guidelines currently include genotypic testing as an equivalent option to phenotypic testing when determining co-receptor usage among patients with HIV RNA >1,000 copies/mL and preferentially for those with HIV RNA ≤1,000 copies/mL.[24]

HIV-1 proviral DNA genotypic tropism testing is available for patients with HIV RNA <1,000 copies/mL. These assays evaluate the HIV-1 proviral DNA integrated within infected cells for CXCR4-utilizing viral strains.[25] As discussed above, caution is advised when using such assays, as their detection limit, concordance with plasma HIV RNA tropism, and clinical utility are not yet fully determined.

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

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

perform, and may have logistic challenges, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII)**.

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

If a CCR5 co-receptor antagonist is being considered in a patient with an undetectable HIV RNA (e.g., in cases of regimen simplification or a toxicity-related switch), a proviral DNA tropism assay can be utilized **(BII)**.[26-28] If CXCR4-utlizing or D/M-tropic viruses are detected, then the CCR5 co-receptor antagonist **should not be used**.

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HLA-B*5701 Screening (Last updated December 1, 2007; last reviewed January 10, 2011)

Panel's Recommendations

- The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) **(AI)**.
- HLA-B*5701-positive patients should not be prescribed ABC **(AI)**.
- The positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**.
- When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR **(CIII)**.

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

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

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

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701.[2,3] Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR.[4] A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele.[5] The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized participants with HIV before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC).[6] The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations).[7]

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

is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

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

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

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

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

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

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

Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

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

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient-related factors, such as active substance abuse, depression, or

the experience of adverse effects; and health system issues, including interruptions in patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART (see Adherence to the Continuum of Care).

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

Panel's Recommendations

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

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

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

Introduction

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

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

Historically, individuals with HIV have had low CD4 counts at presentation to care.[4] However, there have been concerted efforts to increase testing of at-risk individuals and to link individuals with HIV to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts individuals with HIV at risk of both AIDS-defining and certain serious non-AIDS conditions. Furthermore, the magnitude of CD4 recovery is directly correlated with CD4 count at ART initiation. Consequently, many individuals who start treatment with CD4 counts <350 cells/mm^3 never achieve CD4 counts >500 cells/mm^3 after up to 10 years on ART[5,6] and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.[5-7]

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

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

Panel's Recommendations

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

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

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

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

Acute Opportunistic Infections and Malignancies

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

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

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

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

The Need for Early Diagnosis of HIV

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

Evidence Supporting Benefits of Antiretroviral Therapy to Prevent Morbidity and Mortality

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

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

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, participants with HIV who had CD4 counts <800 cells/mm^3 were randomized

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

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

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

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

Evidence Supporting the Use of Antiretroviral Therapy to Prevent HIV Transmission

Prevention of Sexual Transmission

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

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

was virologically suppressed and four other transmissions occurred during virologic failure. These results provide evidence that suppressive ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied. This study, as well as other observational studies and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission.[3,46-49] HPTN 052 was conducted in heterosexual couples and not in populations at risk of HIV transmission via male-to-male sexual contact or needle sharing. In addition, in this clinical trial, adherence to ART was excellent. However, the prevention benefits of effective ART observed in HPTN 052 can reasonably be presumed to apply broadly. Therefore, the Panel recommends that ART be offered to individuals who are at risk of transmitting HIV to sexual partners **(AI)**. Clinicians should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen. Clinicians should also stress that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STIs.

Prevention of Perinatal Transmission

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

Considerations When Initiating Antiretroviral Therapy

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

Optimizing Adherence and Retention in Care

The key to successful ART in maintaining viral suppression is adherence to the prescribed regimen. Treatment failure and resultant emergence of drug resistance mutations may compromise future treatment options. While optimizing adherence and linkage to care are critical regardless of the timing of ART initiation, the evidence thus far indicates that drug resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier.[52] In both the START[8] and TEMPRANO[9] trials, participants randomized to immediate ART achieved higher rates of viral suppression than those randomized to delayed ART. Nevertheless, it is important to discuss strategies to optimize adherence and retention in care with patients before ART initiation.

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

and possibly the type of ART regimen to recommend (see What to Start).

Immediate Antiretroviral Therapy Initiation on the Day of HIV Diagnosis

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

Considerations for Special Populations

Elite HIV Controllers

A small subset of individuals with HIV maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as "elite HIV controllers."[56,57] There are limited data on the role of ART in these individuals. Given the clear benefit of ART regardless of CD4 count from the START and TEMPRANO studies, delaying ART to see if a patient becomes an elite controller after initial diagnosis is strongly discouraged. Nevertheless, significant uncertainty remains about the optimal management of elite controllers who have maintained undetectable viremia in the absence of ART for years. Given that ongoing HIV replication occurs even in elite controllers, ART is clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications. Nonetheless, even elite controllers with normal CD4 counts also have evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS related diseases.[56,58-60] One observational study suggests that elite controllers are hospitalized more often for cardiovascular and respiratory disease than patients from the general population and ART-treated patients.[61] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[62] Whether this potential immunologic benefit of ART in elite controllers outweighs potential ART toxicity and results in clinical benefit is unclear. Unfortunately, randomized controlled trials to address this question are unlikely, given the very low prevalence of elite controllers. Although the START study included a number of participants with very low viral loads and demonstrated the benefit of immediate ART regardless of the extent of viremia, the study did not include a sufficient number of controllers to definitively determine the clinical impact of ART in this specific population. Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.

Adolescents with HIV

Neither the START trial nor the TEMPRANO trial included adolescents. The Panel's recommendation to initiate ART in all patients is extrapolated to adolescents based on the expectation that they will derive benefits from early ART similar to those observed in adults. Historically, compared to adults, youth have demonstrated significantly lower levels of ART adherence and viral suppression, and higher rates of viral rebound following initial viral suppression.[63] Because youth often face multiple psychosocial and other barriers to adherence, their ability to adhere to therapy should be carefully considered when making decisions about ART initiation. Although some adolescents may not be ready to initiate therapy, clinicians should offer ART while providing effective interventions to assess and address barriers to accepting and adhering to therapy. To optimize the benefits of ART for youth, a multidisciplinary care team should provide psychosocial and adherence support (see Adolescents with HIV).[64]

Conclusion

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

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

Panel's Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).
- A pregnancy test should be performed for those of childbearing potential prior to the initiation of antiretroviral therapy **(AIII)**.
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as Recommended Initial Regimens for Most People with HIV (in alphabetical order):
  - Bictegravir/tenofovir alafenamide/emtricitabine **(AI)**
  - Dolutegravir/abacavir/lamivudine[a]—only for patients who are HLA-B*5701 negative **(AI)**
  - Dolutegravir (DTG) plus tenofovir[b]/emtricitabine[a] **(AI)**
  - Raltegravir plus tenofovir[b]/emtricitabine[a] (**BI** for tenofovir disoproxil fumerate, **BII** for tenofovir alafenamide)
- Preliminary data have raised concerns about an increased risk of neural tube defects in infants born to people who were receiving DTG at the time of conception. Before prescribing DTG or another INSTI, please refer to Table 6b for specific recommendations on initiating these drugs as part of initial therapy.
- To address individual patient characteristics and needs, the Panel also provides a list of Recommended Initial Regimens in Certain Clinical Situations (Table 6a).
- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 9 highlights the advantages and disadvantages of different components in a regimen.

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

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

[a] Lamivudine may substitute for emtricitabine or vice versa.

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

Introduction

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

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate (TDF)/FTC, plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 T lymphocyte (CD4) cell count increases in most persons with HIV.[1-3] Emerging data support the use of two-drug regimens, such as

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

Supporting Evidence and Rationale Used for the Panel's Recommendations

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

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

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

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

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

Regimens and medications listed in Table 10 are not recommended as initial ARV. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables presented below and at the end of these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–9 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 10 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Changes Since the Last Revision of the Guidelines

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

INSTI-Based Regimens as Initial Antiretroviral Therapy:

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

NNRTI-Based Regimens as Initial Antiretroviral Therapy:

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

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

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

Protease Inhibitor-Based Regimens as Initial Antiretroviral Therapy:

- Boosted atazanavir (ATV/c or ATV/r) plus ABC/3TC is no longer included in the list of Recommended Initial Regimens in Certain Clinical Situations because it has disadvantages when compared with other regimens in this category. In a randomized trial, ATV/r plus ABC/3TC was less potent than ATV/r plus TDF/FTC in people with HIV RNA >100,000 copies/mL.[10] In a separate randomized trial, ATV/r was less well tolerated than DRV/r.[11]

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

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

Generic Antiretroviral Drugs:

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

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 1 of 2)

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

Recommended Initial Regimens for Most People with HIV
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2 NRTIs: **Note:** For individuals of childbearing potential, see Table 6b before prescribing one of these regimens. • BIC/TAF/FTC **(AI)** • DTG/ABC/3TC[a] **(AI)—if HLA-B*5701 negative** • DTG plus tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC) • RAL[c] plus tenofovir[b]/FTC[a] (**BI** for TDF/FTC, **BII** for TAF/FTC)
Recommended Initial Regimens in Certain Clinical Situations
These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).
INSTI plus 2 NRTIs: **Note:** For individuals of childbearing potential, see Table 6b before prescribing one of these regimens. • EVG/c/tenofovir[b]/FTC (**BI** for both TAF/FTC and TDF/FTC) • RAL[c] plus ABC/3TC[a] **(CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL** Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV) • (DRV/c or DRV/r) plus tenofovir[b]/FTC[a] (AI) • (ATV/c or ATV/r) plus tenofovir[b]/FTCa **(BI)** • (DRV/c or DRV/r) plus ABC/3TC[a] **—if HLA-B*5701 negative (BII)** NNRTI plus 2 NRTIs: • DOR/TDF[b]/3TC **(BI)** or DOR plus TAF[b]/FTC **(BIII)** • EFV plus TDF[b]/FTC[a] (**BI** for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, **BII** for EFV 600 mg plus TAF/FTC) • RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3** Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal: • DTG plus 3TC **(BI)** • DRV/r plus RAL BID **(CI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3** • DRV/r once daily plus 3TC[a] **(CI)**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

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

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

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

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

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BID = twice daily; CD4 = CD4 T lymphocyte; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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

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

Selecting an Initial Antiretroviral Regimen

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

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

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

medications, and the potential for drug-drug interactions (see Tables 7 and 9 for guidance). The Panel's Recommended Initial Regimens for Most People with HIV as listed in Table 6a include one of three INSTIs (BIC, DTG, or RAL) plus two NRTIs. For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI-containing regimens and INSTI-containing regimens, the INSTI was better tolerated and caused fewer treatment discontinuations.[11,14,15]

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

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

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

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

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

Factors to Consider When Selecting an Initial Regimen

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

Initial Characteristics to Consider in All Persons with HIV:

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

Specific Comorbidities or Other Conditions:

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

Regimen-Specific Considerations:

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

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

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

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 cell count <200 cells/mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	A higher rate of virologic failure has been observed in those with low pretreatment CD4 cell counts.
	HIV RNA >100,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels.
	HLA-B*5701 positive or result unknown	**Do not use ABC-containing regimens.**	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
	ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when rapid initiation of ART is warranted	**Avoid NNRTI-based regimens.** **Avoid ABC.** Recommended ART Regimens: • (DRV/r or DRV/c) plus tenofovir[a]/FTC • DTG plus tenofovir[a]/FTC	Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV and DTG is rare, and these drugs have high barriers to resistance. Refer to Table 6b for further guidance before initiating DTG in persons of childbearing potential.
ART-Specific Characteristics	A 1-pill, once-daily regimen is desired	STR Options as Initial ART Include: • BIC/TAF/FTC • DOR/TDF/3TC • DRV/c/TAF/FTC • DTG/ABC/3TC • EFV/TDF/FTC • EFV/TDF/3TC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use RPV-based regimens if HIV RNA is >100,000 copies/mL and CD4 cell count is <200/mm^3. Do not use DTG/ABC/3TC if patient is HLA-B*5701 positive. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential. See Appendix B, Table 10 for ARV dose recommendations in the setting of renal impairment.
	Food effects	Regimens that Can be Taken Without Regard to Food: • BIC-, DOR-, DTG-, or RAL-based regimens	Oral bioavailability of these regimens is not significantly affected by food. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 2 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics, continued	Food effects, continued	Regimens that Should be Taken with Food: • ATV/r- or ATV/c-based regimens • DRV/r- or DRV/c-based regimens • EVG/c/TAF/FTC[a] • EVG/c/TDF/FTC[a] • RPV-based regimens	Food improves absorption of these regimens. RPV-containing regimens should be taken with at least 390 calories of food.
		Regimens that Should be Taken on an Empty Stomach: • EFV-based regimens	Food increases EFV absorption and may increase CNS side effects.
Presence of Other Conditions	Chronic kidney disease (defined as CrCl <60 mL/min)	**Avoid TDF unless the patient has ESRD.** Use ABC or TAF. ABC may be used if patient is HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). TAF may be used if CrCl >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 >200 cells/mm^3 and HIV RNA <100,000 copies/mL)	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 10 for specific dosing recommendations. TAF has less impact on renal function and lower rates of proteinuria than TDF. ATV has been associated with chronic kidney disease in some observational studies. ABC has not been associated with renal dysfunction. Refer to Table 6b for further guidance before initiating an INSTI in persons of childbearing potential.
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 10 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Osteoporosis	**Avoid TDF.** Use ABC or TAF. ABC may be used if patient is HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).	TDF is associated with decreases in BMD along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF and ABC are associated with smaller declines in BMD than TDF.
	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.** Patients on INSTI-based regimens who have pre-existing psychiatric conditions should be closely monitored. Some ARVs are contraindicated and some psychiatric medications need dose adjustments when coadministered with certain ARVs.	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 3 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	HAD	**Avoid EFV-based regimens if possible.** Favor DTG- or DRV-based regimens.	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.
	Medication-assisted treatment for opioid dependence	Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring is recommended, as medications used to treat opioid dependence may need to be adjusted in some patients.	EFV reduces methadone concentrations and may lead to withdrawal symptoms. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations.
	High cardiac risk	Consider avoiding ABC- and LPV/r -based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen. BIC-, DOR-, DTG-, RAL-, or RPV-based regimens may be considered for those with high cardiac risk.	An increased CV risk with ABC has been observed in some studies. 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.
	Cardiac QTc interval prolongation	Consider avoiding EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.	High EFV or RPV concentrations may cause QT prolongation.
	Hyperlipidemia	The Following ARV Drugs Have Been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c BIC, DOR, DTG, RAL, and RPV have fewer lipid effects.	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.
	Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care	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.	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.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Pregnancy	Until more information is available, **do not initiate a DTG-based regimen** for those who are pregnant and within 12 weeks post-conception, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Refer to Table 6b and the Perinatal Guidelines for further guidance on ARV use during pregnancy.	
	Patients of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception	Until more information is available, **do not initiate a DTG-based regimen in these patients**, because preliminary data suggest that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception.[6,7] Refer to Table 6b for further guidance before initiating an INSTI.	
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC, whenever possible. If TDF and TAF Are Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug that is active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	
	Treating TB disease with rifamycins	**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).	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 21a, 21b, 21c, 21d and 21e) and TB/HIV Coinfection for information on ARV use with rifamycins.

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

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

Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

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

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

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

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

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

Summary

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

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

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug[10,29,30] (see also the discussion in the DTG section).[31]

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each was used in combination with either EFV or ATV/r. In patients with baseline HIV RNA ≥100,00 copies/mL, there was a significantly shorter time to virologic failure with ABC/3TC than with TDF/FTC regardless of whether the third active drug was EFV or ATV/r.[10] In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. Virologic efficacy was similar in the two study arms, including in a subgroup with HIV RNA ≥100,000 copies/mL.[30]
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701–negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. At week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants than among TDF/FTC-treated participants.[29]

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

- Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of EVG/c/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.
  - TAF/FTC was virologically noninferior to TDF/FTC at week 48 (92% vs. 90% of participants achieved plasma HIV RNA <50 copies/mL, respectively),[32] but TAF/FTC was superior to TDF/FTC at week 144 (84.2% vs. 80%), largely driven by a higher rate of treatment discontinuation in the TDF arm.[33]
  - Participants in the TAF arm had significantly smaller reductions in BMD at the spine and hip than those in the TDF arm through 144 weeks.[33] They also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through week 96.[34] Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at 96 weeks, with no change in total cholesterol to HDL ratio.[35]

- Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC each administered in combination with boosted DRV in ART-naive subjects:
  - A Phase 2 study of coformulated DRV/c plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% vs. 74%) in treatment-naive patients.[36] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.
  - The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At 48 weeks, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[37]
- One analysis evaluated data from 11 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF or TAF when either drug was taken with or without PK boosters (RTV or COBI). There were no significant differences between unboosted TDF and TAF in terms of virologic efficacy or in the number of participants who discontinued treatment due to renal or bone adverse events or fractures. However, bone- and renal-related toxicities were more pronounced when TDF was used in combination with RTV or COBI.[28]
- To assess the ability of TAF to maintain HIV and HBV suppression, 72 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 log10 IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[38] In this study, 96% of participants were on a TDF/FTC-containing regimen prior to the switch. Key results of the study showed that:
  - Those who switched to EVG/c/TAF/FTC maintained HIV suppression: 94.4% and 91.7% of participants at 24 and 48 weeks, respectively. At 24 and 48 weeks, 86.1% and 91.7% of participants had HBV DNA <29 $\log_{10}$ IU/mL.
  - Decreases in markers of proximal tubular proteinuria and biomarkers of bone turnover were seen in those who switched to EVG/c/TAF/FTC.[38]

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

Abacavir/Lamivudine (ABC/3TC)

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

Adverse Effects

Hypersensitivity Reactions:

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

Cardiovascular Risk:

- An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.[19,44]

- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[45-51] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[18,52-55]
- An analysis of data from NA-ACCORD found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.[56]
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations:

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

The Panel's Recommendations:

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

Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

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

Adverse Effects

Renal and Bone Effects:

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

Lipid Effects:

- In randomized controlled trials in ART-naive patients, as well as in switch studies (described below), levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and TDF. The clinical significance of this finding is not clear.[32,57,58]

Other Factors and Considerations:

- TAF/FTC is available in FDCs with DRV/c, EVG/c or RPV, allowing the regimens to be administered as a single pill taken once daily with food.
- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see the INSTI section below).
- TAF-containing regimens are approved for patients with eGFR ≥30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in patients on hemodialysis with eGFRs <15 mL/min.[59]
- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).[38]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[60] and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with BIC, DTG, and RAL.

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

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

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[76,77] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)[78] and pre-existing renal impairment.[79] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that there is a greater risk of renal dysfunction when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.[77,79-83]
- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC with PK boosting.[28]

Bone Effects:

- While initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[84,85] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above).
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[86]
- Adverse bone outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that fractures and discontinuation due to bone adverse events occur more frequently among patients who take TDF/FTC with PK boosting.[28]

Other Factors and Considerations:

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.
- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring). In patients who have pre-existing renal insufficiency (creatinine clearance [CrCl] <60 mL/min),[87] use of TDF should generally be avoided. If TDF is used, a dose adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 10 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HIV/HBV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most persons with HIV when combined with DTG or RAL. See Table 6a for recommendations regarding use of TDF/FTC with other drugs.
- TDF should be used with caution or avoided in patients with renal disease and osteoporosis.
- Specific attention should be given to renal and bone safety monitoring when TDF is used, especially with PK boosters. Boosters should be avoided when possible in patients taking TDF.

Integrase Strand Transfer Inhibitor–Based Regimens

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

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

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

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

	BIC	DTG	EVG	RAL
Dosing Frequency	Once daily	Once Daily: • In ART-naive or INSTI-naive persons Twice Daily: • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In INSTI-experienced persons with certain INSTI DRMs	Once daily; requires boosting with COBI	• 400 mg BID, *or* • 1200 mg (two 600-mg tablets) once daily
STR Available for ART-Naive Patients	BIC/TAF/FTC	DTG/ABC/3TC	• EVG/c/TAF/FTC • EVG/c/TDF/FTC	No
Available as a Single-Drug Tablet	No	Yes	No	Yes
Approved for ART-Experienced Patients	No	Yes, with BID dosing for patients with some INSTI DRMs	No	Yes, for patients with DRM to PI/r or NNRTIs, but no DRM to INSTIs
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but no clinical trial data are available	Yes, for some isolates; effective with 50 mg BID dose	No	No
Adverse Effects	Nausea, diarrhea (GI disturbance greater with EVG/c), headache, insomnia. Depression and suicidality are rare, occurring primarily in patients with pre-existing psychiatric conditions.			
	↑ CPK (4%)	Hypersensitivity, hepatotoxicity, ↑ CPK, myositis	↑ TG, ↑ LDL	↑ CPK, myopathy, hypersensitivity, SJS/TEN
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)	EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor	No
Chelation with Polyvalent Cation Supplements and Antacids	Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 21d for recommendations regarding dosing separation of INSTIs and these drugs.			
Other Key Potential Drug Interactions	UGT1A1 substrate, OCT2 and MATE1 inhibitor	p-gp substrate, UGT1A1 substrate	EVG is a UGT1A1 substrate; COBI is a p-gp inhibitor	UGT1A1 substrate

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

Summary

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

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

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

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

Bictegravir (BIC)

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

Efficacy in Clinical Trials:

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at week 48.
  - The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At week 48, 89% of participants in the BIC arm and 93% of those in the DTG arm achieved HIV RNA <50 copies/mL ($P = 0.12$).[31]
  - The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At week 48, 92.4% of participants in the BIC/TAF/FTC arm and 93% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL ($P = 0.78$).[5]

Adverse Effects:

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

Other Factors and Considerations:

- BIC is a CYP3A4 substrate and a UGT1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John's wort should also be avoided.[88]
- BIC is an inhibitor of the drug transporters OCT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, it is unlikely to affect the metabolism of medications that are CYP3A4 substrates.
- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids, or calcium or iron supplements). See Table 21d for dosing recommendations when using BIC with these products.
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are typically observed within the first 4 weeks (with a median increase of 0.10 mg/dL after 48 weeks). This effect on creatinine secretion is similar to that seen with other medications used in people with HIV, including DTG and COBI.
- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations, and BIC should not be used in these individuals until more data are available.
- BIC and DTG share a similar chemical structure. It is unclear whether DTG is the only INSTI with the potential to cause NTDs or if other INSTIs also carry this risk.

The Panel's Recommendation:

- On the basis of clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a Recommended Initial Regimen for Most People with HIV **(AI)**.
- Because there are no safety data for the use of BIC around the time of conception to guide evidence-based recommendations, a similar approach to the one outlined for DTG should be discussed before considering the use of BIC-containing ART in those of childbearing potential. The use of BIC-containing ART is not recommended during pregnancy.

Dolutegravir (DTG)

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

Efficacy in Clinical Trials

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

DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

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

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

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

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

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

DTG plus Two NRTIs versus DTG plus 3TC:

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

Adverse Effects:

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

adverse events has not been defined.

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

Other Factors and Considerations:

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment (mean increase in serum creatinine was 0.11 mg/dL after 48 weeks).
- DTG has fewer drug interactions than EVG/c. See Drug-Drug Interactions for specific drug-drug interactions that require dosage adjustment.
- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see Drug-Drug Interactions). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have not been reported in patients receiving DTG as part of a three-drug regimen for initial therapy, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel's Recommendations:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI)**, TAF/FTC **(AI)**, or TDF/FTC **(AI)** as a Recommended Initial Regimen for Most People with HIV.
- A pregnancy test should be performed for those of childbearing potential prior to initiation of DTG **(AIII)**.
- For those of childbearing potential who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG with the individual **(BIII)**.
- Until more information is available, DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception **(AII)**, *or*
  - Who are of childbearing potential and who are planning to become pregnant **(AII)** or who are sexually active and not using effective contraception **(AIII)**.

Raltegravir (RAL)

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

Efficacy in Clinical Trials

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

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label, randomized trial.
  - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in

combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[66] RAL was superior to EFV at 4 and 5 years,[69,99] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.

- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.
- The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads ≥100,000 copies/mL and 125 participants with baseline viral loads <100,000 copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, there was no difference in virologic response between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.[70]
- ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the PI/r arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[11]

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

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

Adverse Effects:

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.[101]
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see the discussion under DTG).[97,102]

Other Factors and Considerations:

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients.
- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids **is not recommended**. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See Table 21d for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.

The Panel's Recommendations:

- On the basis of these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets)

once daily or as 400 mg twice daily plus TDF/FTC **(BI)** or TAF/FTC **(BII)** as a Recommended Initial Regimen for Most People with HIV.

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

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

Elvitegravir (EVG)

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

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ART-naive participants has been evaluated in two randomized, double-blind active-controlled trials.
  - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.[103]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[104]
  - In a randomized, blinded trial performed in women with HIV, EVG/c/TDF/FTC had superior efficacy when compared to ATV/r plus TDF/FTC, in part because of a lower rate of treatment discontinuation.[15]
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR ≥50 mL/min.[32,35]
  - 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.[33]

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[103,104]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[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).[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.[107] Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be closely monitored and evaluated for evidence of TDF-related proximal renal tubulopathy.[83]
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.[83]
- EVG/c/TAF/FTC **is not recommended** for patients with pretreatment estimated CrCl <30 mL/min.
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.[103,104] These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.

The Panel's Recommendation:

- On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as Recommended Initial Regimens in Certain Clinical Situations **(BI)**. EVG/c/TAF/FTC should only be used in people with estimated CrCl ≥30 mL/min; EVG/c/TDF/FTC should only be used in people with estimated CrCl ≥70 mL/min.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

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

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

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

Summary

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

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

Doravirine (DOR)

Efficacy in Clinical Trials

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

DOR-Based Regimen versus EFV-Based Regimen:

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

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

- In DRIVE-FORWARD, 769 participants received DOR or DRV/r once daily along with two investigator-selected NRTIs, either ABC/3TC or TDF/FTC.[8]
- At 48 weeks, DOR was found to be noninferior to DRV/r when these drugs were administered with two NRTIs. Eighty-four percent of study participants receiving DOR achieved HIV RNA <50 copies/mL at 48 weeks, compared to 80% of participants receiving DRV/r.
- Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.
- At week 96, DOR was superior to DRV/r in terms of virologic suppression;[112] there was a higher rate of discontinuation in the DRV/r group.

- Genotype resistance results were reported for seven and eight participants with virologic failure in the DOR and DRV/r arms, respectively. No drug resistance mutations were detected in either group.
- Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol and triglycerides were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations:

- DOR is available as a single-drug, 100-mg tablet[113] and as part of an STR that contains DOR/TDF/FTC 100 mg/300 mg/300 mg[114] and is dosed once daily, with or without food.
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 21b).
- DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.[115]
- DOR-based regimens have not been directly compared to INSTI-based regimens in clinical trials.
- There are currently no data on the safety of DOR use during pregnancy.

The Panel's Recommendations:

- On the basis of the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC **(BI)** and DOR plus two NRTIs (**BI** for TDF/FTC and **BIII** for TAF/FTC) as Recommended Initial Regimens in Certain Clinical Situations.
- Because the number of participants who received DOR plus ABC/3TC is much lower than the number who received TDF/FTC plus DOR, the Panel considers ABC/3TC plus DOR to be an option for initial therapy, but the Panel has less confidence in this regimen than in the other DOR-containing regimens listed above **(CI)**.

Efavirenz (EFV)

Efficacy in Clinical Trials:

- Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. In clinical trials, EFV-based regimens have demonstrated superiority or noninferiority to several comparator regimens in ART-naive patients.
- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[116]
- In the ECHO and THRIVE studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.[117]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[103]
- The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 48

weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.

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

- In the SINGLE trial, a DTG-based regimen was superior to EFV at the primary endpoint of viral suppression at week 48.[31]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks,[66] but RAL was superior to EFV at 4 and 5 years,[69,99] 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 coinfection are lacking.

Adverse Effects:

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

Other Factors and Considerations:

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.

- EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily STR tablet that uses 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children who weigh ≥35 kg.[128,129]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6; therefore, it may potentially interact with other drugs that use the same pathways (see Tables 21b, 22a, and 22b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.[130] A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).[131]
- Screening for depression and suicidality is recommended for people with HIV who are taking a regimen that includes EFV.

The Panel's Recommendations:

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

Rilpivirine (RPV)

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

Efficacy in Clinical Trials:

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

study. In this study, participants taking the coformulated drug had plasma concentrations of RPV, FTC, and TAF 25 mg that were similar to concentrations seen in participants who received RPV as the single-drug tablet and TAF/FTC when given as part of the FDC of EVG/c/TAF 10 mg/FTC.[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.[133] However, this combination has not been studied in ART-naive individuals, and it **is not recommended** for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is **contraindicated** in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see Drug-Drug Interactions for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug-Drug Interactions).
- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations:

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as Recommended Initial Regimens in Certain Clinical Situations.
- Use of RPV with TAF/FTC **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 cell counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

Protease Inhibitor-Based Regimens

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

	ATV	DRV
Dosing Frequency	Once daily	• Once daily for PI-naive patients • Twice daily for PI-experienced patients with certain PI mutations
PK Boosting	PK-boosting with RTV or COBI is generally recommended. Unboosted ATV is also FDA-approved for ART-naive patients.	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	• ATV/c	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	• Jaundice • Indirect hyperbilirubinemia • Cholelithiasis • Nephrolithiasis • PR prolongation	• Skin rash • Increase in serum transaminases • Hyperlipidemia • A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate, inhibitor	CYP34A substrate, inhibitor
Other Significant Drug Interactions	ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 21a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.	N/A

Key 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 5.

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 ART-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR achieving HIV RNA levels <50 copies/mL compared with 84% of participants who received DRV/r.

Adverse Effects:

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

Other Factors and Considerations:

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

The Panel's Recommendations:

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

Darunavir/Cobicistat (DRV/c)

A combination of DRV 800 mg with COBI 150 mg is bioequivalent to DRV 800 mg with RTV 100 mg in healthy volunteers, based on the maximum concentration and area under the concentration time curve for DRV.[138] Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that of DRV combined with RTV, bioequivalence for the C_{min} was not achieved.[139]

Efficacy in Clinical Trials:

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the STR DRV/c/TAF/FTC and DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of the study (91% and 88%, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group. In the DRV plus TAF/FTC arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.[37]
- In a single-arm trial in which most of the patients were treatment-naive (94%), the coformulated DRV/c 800 mg/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.[140]

Adverse Effects:

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

Other Factors:

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

The Panel's Recommendations:

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

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

Efficacy in Clinical Trials:

ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs

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

ATV/r plus Two NRTIs versus EFV plus Two NRTIs

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

ATV/r plus Two NRTIs versus INSTI plus Two NRTIs

- In a study that compared ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.[104] A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.[15] At week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm discontinued therapy because of adverse events, compared to five women in the INSTI arm.
- In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, DTG was found to have a rate of virologic suppression (<50 copies/mL) that was noninferior to the rate seen in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.[92]

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

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

ATV/c versus ATV/r plus Two NRTIs

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

Adverse Effects:

- The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.[145]
- Nephrolithiasis,[146-148] nephrotoxicity,[21] and cholelithiasis[149] have also been reported in patients who received ATV.
- Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

Other Factors and Considerations:

- ATV/c and ATV/r are dosed once daily and with food.
- ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly PPIs) may impair absorption of ATV. Table 21a provides

recommendations for use of ATV/c or ATV/r with these agents.

- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug-Drug Interactions).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[18-20,23] Another study of an observational cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens compared with participants receiving other regimens.[22] Further study is needed.

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC **(BII)** or TDF/FTC **(BI)** as Recommended Initial Regimens in Certain Clinical Situations.
- ATV/c or ATV/r plus ABC/3TC is no longer included in the list of Recommended Initial Regimens in Certain Clinical Situations, because it has disadvantages when compared with other regimens in this category. In a randomized trial, when combined with ATV/r, ABC/3TC was less potent than TDF/FTC in people with HIV RNA >100,000 copies/mL.[10]
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

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

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

Strategies Supported by Evidence from Clinical Trials

Dolutegravir plus Lamivudine (DTG plus 3TC)

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

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

The Panel's Recommendation:

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

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

- In the ANDES trial, 145 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.[25] The dual- and triple-therapy groups had similar rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL (91% and 92%, respectively).

The Panel's Recommendation:

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

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

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 cell counts <200 cells/mm^3, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.[24] High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.[153,154]

The Panel's Recommendation:

- On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 cell counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

A Nucleoside-Limiting Regimen that is Efficacious but has Disadvantages

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

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

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

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

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

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

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI	**ABC/3TC**	• Coformulated with DTG • Generic formulations are available for ABC/3TC, ABC, and 3TC.	• May cause life-threatening HSRs in patients who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, EVG/c, or RPV • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for patients with eGFR ≥30 mL/min	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids.

	TDF/3TC	• Coformulated with DOR and EFV
		• Available as the following generic formulations:
		  • TDF
		  • 3TC
		  • TDF/3TC
		  • EFV/TDF/3TC
		• Long-term clinical experience
		• Active against HBV
			• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters.
			• Osteomalacia has been reported as a consequence of proximal tubulopathy.
			• Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.

	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with lower lipid levels than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
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 21d. • Inhibits tubular secretion of creatinine without affecting glomerular function. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug interactions.
	DTG	• 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 21d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions).
	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 21d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Food requirement. • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, continued	**RAL**	• Compared to other INSTIs, has longest post-marketing experience • 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 21d. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • 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 21b, 22a and 22b). • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.
	EFV	• EFV 600 mg is coformulated with TDF/FTC and TDF/3TC • EFV 400 mg is coformulated with TDF/3TC • EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA	• 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 21b and 22a). • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)

NNRTI, continued	**RPV**	• Coformulated with TDF/FTC and TAF/FTC
		• 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/mm^3 because of higher rate of virologic failure in these patients.
			• Depression and suicidality
			• QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.
			• Rash
			• Transmitted resistance is more common than with PIs and INSTIs.
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.
			• Potential for CYP450 drug interactions (see Tables 21b and 22a).
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption.
			  • **Contraindicated** with PPIs.
			  • Use with H2 antagonists or antacids with caution (see Table 21a for detailed dosing information).

PIs	**ATV/c** or **ATV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs • ATV/c and ATV/r have similar virologic activity and toxicity profiles • Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion. • Individual ATV and RTV components available as generics	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 21a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 21a).
	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 21a). • Increased CV risk reported in one observational cohort study.

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

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs, continued	**DRV/c** (Specific considerations)	• Coformulated as DRV/c and DRV/c/TAF/FTC	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • 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.
	LPV/r	• Only RTV-coformulated PI • No food requirement	• 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 21a).

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

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

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

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

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

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

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

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

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

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

Antiretroviral Drugs Not Recommended

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

Antiretroviral Regimens Not Recommended

Monotherapy

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

Dual-NRTI Regimens

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

Triple-NRTI Regimens

Triple-NRTI regimens have suboptimal virologic activity[10-12] or a lack of data **(AI)**.

Antiretroviral Components Not Recommended

Atazanavir plus Indinavir

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

Cobicistat plus Ritonavir as Pharmacokinetic Enhancers

This combination may be prescribed inadvertently, which may result in additive CYP3A4 enzyme inhibition and may further increase the concentrations of ARV drugs or other concomitant medications (see Tables 21a and 21d).

Didanosine plus Stavudine

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

Didanosine plus Tenofovir Disoproxil Fumarate

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

Two Non-Nucleoside Reverse Transcriptase Inhibitor Combinations

Excess clinical adverse events and treatment discontinuation were reported in patients randomized to receive treatment with two non-nucleoside reverse transcriptase inhibitors (NNRTIs).[21] Efavirenz (EFV) and nevirapine (NVP) are enzyme inducers, and both of these drugs can reduce concentrations of etravirine (ETR) and rilpivirine (RPV) **(AI)**.[22]

Emtricitabine plus Lamivudine

Both drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo* **(AIII)**.[23]

Etravirine plus Unboosted Protease Inhibitor

ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established **(AII)**.[22]

Etravirine plus Fosamprenavir/Ritonavir

ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established **(AII)**.[22]

Etravirine plus Tipranavir/Ritonavir

Tipranavir/ritonavir (TPV/r) significantly reduces ETR concentrations **(AII)**.[22]

Nevirapine Initiated in ARV-Naive Women with CD4 Counts >250 cells/mm^3 or in ARV-Naive Men with CD4 Counts >400 cells/mm^3

Initiating NVP in ART-naive individuals with CD4 counts above these thresholds increases the risk of symptomatic, and sometimes life-threatening, hepatic events.[24-26] ART-experienced patients can safely switch to NVP if they have CD4 counts above these thresholds as a result of receiving effective ART **(BI)**.[27]

Unboosted Darunavir, Saquinavir, or Tipranavir

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

Stavudine plus Zidovudine

These NRTIs are antagonistic *in vitro*[28] and *in vivo*[29] **(AII)**.

Tenofovir Alafenamide plus Tenofovir Disoproxil Fumarate

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

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Management of the Treatment-Experienced Patient

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

Panel's Recommendations

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

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

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

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

Virologic Response Definitions

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

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

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

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

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

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

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

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

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

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

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

Causes of Virologic Failure

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

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

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

HIV-Related Factors

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

Antiretroviral Regimen-Related Factors

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

Managing Patients with Virologic Failure

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

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

Key Factors to Consider When Designing a New Antiretroviral Regimen

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

Antiretroviral Strategies

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

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

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

Addressing Patients with Different Levels of Viremia

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

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

- Assessing the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence.
- Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI; see Adverse Effects of Antiretroviral Agents).
- Reviewing food requirements for each medication and assessing whether the patient adheres to the requirements.
- Assessing whether there is a recent history of gastrointestinal symptoms (e.g., vomiting or diarrhea) that may result in short-term malabsorption.
- Reviewing concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions and Tables 21a–22b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
- Considering therapeutic drug monitoring if PK drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected.
- Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for >4 weeks before testing?).
  - If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen.
  - If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective but more tolerable regimen.
  - Repeat viral load testing 2 to 4 weeks after treatment is resumed or started; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged **(CIII)**.

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

Managing Virologic Failure in Different Clinical Scenarios

See Table 11 for a summary of these recommendations.

Virologic Failure with First Antiretroviral Regimen

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

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

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

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

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

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

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

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

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

Second-Line Regimen Failure and Beyond

Drug Resistance with Fully Active Antiretroviral Therapy Options

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

Multidrug Resistance without Fully Active Antiretroviral Therapy Options

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

Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. When DTG is the only treatment option, or one of few treatment options, providers should counsel individuals who are pregnant or of childbearing potential about the possible association between NTDs and DTG use during conception. Providers should also discuss the risks of persistent viremia in the patient and the risk of HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after careful consideration of all these risks.

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

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

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

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

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

Table 11. Antiretroviral Options for Patients with Virologic Failure

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

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

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

Table 11. Antiretroviral Options for Patients with Virologic Failure

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

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

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

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

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

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

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

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

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

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

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

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

Summary

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

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

Panel's Recommendations

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

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

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

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

Poor CD4 Cell Recovery

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

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

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

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

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

Persistent Immune Activation and Inflammation

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

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

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

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

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

Panel's Recommedations

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

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

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

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

Reasons to Consider Regimen Switching in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short- or long-term toxicity (see Adverse Effects of Antiretroviral Agents and Table 18 for a more in-depth discussion of possible toxicities)
- To prevent or mitigate drug-drug interactions (see Drug-Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur (see the Perinatal Guidelines)
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)

General Principles of Regimen Switching

Maintain Viral Suppression

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

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

Careful Review of Antiretroviral History Before Switch

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

Assess Prior Resistance Before Switch

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

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

Switching in a Person with Hepatitis B Virus Coinfection

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

Assess for Potential Drug Interactions

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

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

Assess for Potential for Pregnancy

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

Until more information is available:

- Clinicians should discuss the possible association between NTDs and DTG use during conception and the benefits of DTG for HIV treatment with individuals of childbearing potential; clinicians should also provide appropriate counseling so that the individual can make an informed decision about the use of DTG **(AIII)**.
- DTG **is not recommended** for those:
  - Who are pregnant and within 12 weeks post-conception;
  - Who are of childbearing potential, sexually active, and not using effective contraception; *or*
  - Who are contemplating pregnancy.
- It is unknown whether the possible risk of NTDs associated with DTG use at the time of conception is shared by other integrase strand transfer inhibitors (INSTIs) (i.e., a class effect).
- BIC is structurally similar to DTG, but there are no safety data on the use of BIC around the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be taken before considering BIC-containing ART.

Monitoring after Switch

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

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

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

Strategies with Good Supporting Evidence

Three-Drug Regimens

Within-Class Switches

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

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

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

Between-Class Switches

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

Some examples of between-class switch strategies are:

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

Two-Drug Regimens

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

Dolutegravir plus Rilpivirine

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

Ritonavir-Boosted Protease Inhibitor plus Lamivudine or Emtricitabine

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

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

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

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

Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir

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

Strategies with Some Supporting Evidence

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

Boosted Protease Inhibitor plus Integrase Strand Transfer Inhibitor

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

Dolutegravir plus Lamivudine

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

Clinical Trials

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

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

Observational Studies

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

Strategies Not Recommended

Boosted Protease Inhibitor Monotherapy

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

Dolutegravir Monotherapy

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

Boosted Atazanavir plus Raltegravir

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

Maraviroc plus Boosted Protease Inhibitor

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

Maraviroc plus Raltegravir

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

Monitoring after Treatment Changes

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

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

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

Short-Term Therapy Interruptions

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

Unanticipated Short-Term Therapy Interruption

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

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

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

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

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

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

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

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

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

Planned Long-Term Therapy Interruptions

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

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

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

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Considerations for Antiretroviral Use in Special Patient Populations

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

Panel's Recommendations

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

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

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

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

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

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

Diagnosing Acute HIV-1 Infection

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

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

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

Treating Early HIV-1 Infection

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

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

Considerations When Treating Early HIV-1 Infection

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

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

Treating Early HIV-1 Infection During Pregnancy

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

Treatment Regimens for Early HIV-1 Infection

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

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

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

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

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

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

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

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

Patient Follow-Up

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

Duration of Therapy for Early HIV-1 Infection

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

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

Suspicion of Acute HIV-1 Infection:

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

Evaluation/Diagnosis of Acute HIV-1 Infection:

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

Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:

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

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

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

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

Key Summary and Panel's Recommendations

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

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

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

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

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

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

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

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

Antiretroviral Therapy Considerations in Adolescents

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

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

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

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

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

It is not known whether this possible risk of NTDs is shared by other integrase strand transfer inhibitors (i.e., a class effect). Bictegravir (BIC) is structurally similar to DTG, but there are no safety data on the use of BIC near the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART. Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Adherence Concerns in Adolescents

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

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

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

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

Difficult Adherence Problems

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

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

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

Special Considerations in Adolescents

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

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

Transitioning Care

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

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

Interventions to facilitate transition should be implemented early to ensure a successful transition.[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.

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HIV-2 Infection (Last updated July 10, 2019; last reviewed July 10, 2019)

Key Considerations and Recommendations
• The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and lower mortality rate than HIV-1 infection. However, progression to AIDS and death will occur in the majority of individuals without treatment.
• No randomized controlled trials have addressed when a person with HIV-2 should start antiretroviral therapy (ART) or which regimens are most effective for initial or second-line ART when treating HIV-2; thus, the optimal treatment strategy is not well defined.
• Existing data on the treatment of HIV-2, and extrapolation from data on the treatment of HIV-1, suggest that ART should be started at or soon after HIV-2 diagnosis to prevent disease progression and transmission of HIV-2 to others **(AIII)**.
• Quantitative plasma HIV-2 RNA viral load testing for clinical care is available and should be performed before initiation of ART **(AIII)**.
• HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors and to enfuvirtide; therefore, these drugs **should not be included** in ART regimens for HIV-2 infection **(AII)**.
• Patients with hepatitis B virus (HBV)/HIV-2 coinfection should be prescribed ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**.
• Initial ART regimens for ART-naive patients who have HIV-2 monoinfection or HIV-1/HIV-2 coinfection should include an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs) **(AII)**. An alternative regimen is a boosted protease inhibitor (PI) that is active against HIV-2 (darunavir or lopinavir) plus two NRTIs **(BII)**.
• HIV-2 RNA, CD4 T lymphocyte (CD4) cell counts, and clinical status should be used to assess treatment response **(AIII)**. Unlike persons with HIV-1, persons with HIV-2 should continue to undergo periodic CD4 cell count testing even if their viral loads are persistently suppressed, because disease progression can occur despite an undetectable viral load.
• Resistance-associated viral mutations to INSTIs, PIs, or NRTIs may develop in persons with HIV-2 while they are on ART. However, no validated HIV-2 genotypic or phenotypic antiretroviral resistance assays are approved for clinical use.
• In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Overview

HIV-2 infection is endemic in West Africa, with certain countries experiencing a population prevalence of >1%. The possibility of HIV-2 infection should be considered when treating persons of West African origin, persons who have had sexual contact or shared needles with persons of West African origin, and persons who reside in countries with strong socioeconomic ties to West Africa (e.g., France, Spain, Portugal, and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India). Globally, it has been estimated that one million to two million individuals have HIV-2, a number that includes people with HIV-1/HIV-2 dual infection. However, current and accurate prevalence data are scarce, and neither the Joint United Nations Programme on HIV and AIDS nor the World Health Organization have a formal surveillance system for HIV-2.[1]

Clinical Course of HIV-2 Infection

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma viral loads, and a lower mortality rate than HIV-1 infection.[2,3] However, without effective antiretroviral therapy (ART), HIV-2 infection will progress to AIDS and death in the majority of individuals.[4] Concomitant HIV-1 and HIV-2 infection may occur, and the possibility of this coinfection should be considered when treating persons from areas with a high prevalence of HIV-2.

Diagnostic and Monitoring Assays for HIV-2 Infection

In the appropriate epidemiologic setting, HIV-2 infection should be suspected in persons who have clinical

conditions that suggest HIV infection but who have atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).[5] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in persons who have serologically confirmed HIV infection but who have low or undetectable HIV-1 RNA levels, or in those who have declining CD4 T lymphocyte (CD4) cell counts despite apparent virologic suppression on ART.

The 2014 Centers for Disease Control and Prevention guidelines for HIV diagnostic testing[6] recommend using an HIV-1/HIV-2 antigen/antibody combination immunoassay for initial testing and using an HIV-1/HIV-2 antibody differentiation immunoassay for subsequent testing. The Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories) is approved by the Food and Drug Administration (FDA) to differentiate HIV-1 infection from HIV-2 infection. The Multispot HIV-1/HIV-2 Rapid Test is no longer available. Commercially available HIV-1 RNA assays do not reliably detect or quantify HIV-2 RNA.[7] Quantitative HIV-2 RNA testing is available at the University of Washington (UW)[8] and the New York State Department of Health (NYSDOH).[9] HIV-2 nucleic acid amplification test-based (total DNA/RNA) diagnostic testing is available for clinical care at UW.[10] However, it is important to note that up to one-third of persons with untreated HIV-2 infection will have HIV-2 RNA levels below the limits of detection (10 copies/mL for UW testing and 7 IU/mL for NYSDOH testing); some of these persons will have clinical progression and CD4 cell count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are approved by the FDA for clinical use. HIV-2 genotypic ARV resistance assays are available at UW for research use only.

Treatment of HIV-2 Infection

To date, no randomized controlled trials that address when to start ART or the choice of initial or subsequent ART regimens for HIV-2 infection have been completed;[11] thus, the optimal treatment strategy has not been defined. Existing data on the treatment of HIV-2 and extrapolation from data on the treatment of HIV-1 suggest that ART should be started at or soon after HIV-2 diagnosis in order to prevent disease progression and transmission of HIV-2 to others **(AIII)**. However, CD4 cell recovery in persons with HIV-2 who are on ART is generally poorer than that observed in persons with HIV-1.[12,13]

Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs); however, HIV-2 is more likely to develop resistance to NRTIs than HIV-1.[14] HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs);[15] thus, NNRTI-based regimens are not recommended for treatment of HIV-2 **(AII)**. Several small studies in individuals with HIV-2 infection have reported poor responses to dual-NRTI regimens[16,17] or regimens that contain an NNRTI plus two NRTIs.[18,19] Clinical data on the effectiveness of triple-NRTI regimens are conflicting.[20,21]

Integrase strand transfer inhibitor (INSTI)-based regimens or protease inhibitor (PI)-based regimens are treatment options for persons with HIV-2. As discussed below, two single-arm clinical trials showed favorable outcomes in patients who received INSTI-based regimens; data regarding the efficacy of PI-based regimens primarily come from observational reports. A randomized controlled trial comparing raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to lopinavir/ritonavir (LPV/r) plus TDF/FTC is currently underway (FIT-2; NCT02150993).

INSTI-Based Regimens

All FDA-approved INSTIs—RAL, elvitegravir (EVG), dolutegravir (DTG), and bictegravir—have potent activity against HIV-2 *in vitro*.[22-26] INSTI-based regimens have shown favorable treatment responses in observational studies.[27-29] Two single-arm, open-label clinical trials have assessed the effectiveness of INSTI-based regimens in ART-naive individuals with HIV-2. One study evaluated RAL plus TDF/FTC, and the other evaluated EVG/cobicistat/TDF/FTC. Both studies demonstrated favorable clinical and immuno-virologic results at 48 weeks, providing the best evidence to date for HIV-2 treatment recommendations.[30,31]

PI-Based Regimens

In general, regimens that contain boosted PIs that are active against HIV-2 (and that also include two NRTIs) have resulted in more favorable virologic and immunologic responses than regimens that consist of only two or three NRTIs.[12,13,21,32] Darunavir (DRV), LPV, and saquinavir are more active against HIV-2 than other approved PIs.[33-35] Older, unboosted PI-based regimens, including nelfinavir or indinavir plus zidovudine and lamivudine, and atazanavir-based regimens have shown poor clinical success rates.[11,16,17,36,37]

Amongst the entry inhibitors, HIV-2 is intrinsically resistant to enfuvirtide.[38] The CCR5 antagonist maraviroc appears to be active against some HIV-2 isolates;[39] however, there are no FDA-approved assays that can determine HIV-2 co-receptor tropism, and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[40] There are no data yet on the activity of ibalizumab against HIV-2.

Some national and international guidelines have recommended specific preferred and alternative drug regimens for initial and second-line ART for HIV-2 infection;[41-44] however, there are currently no comparative randomized controlled clinical trial data that support the effectiveness of a specific recommended regimen.

Until there are more definitive data on outcomes, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends the following regimens for individuals with HIV-2 monoinfection or HIV-1/HIV-2 dual infection:

- A regimen that contains one INSTI plus two NRTIs is the recommended initial ART regimen for most individuals with HIV-2 infection **(AII)**. Recent observational data suggest an increased risk of neural tube defects in infants born to mothers who were receiving DTG at the time of conception. For recommendations on the use of DTG in those of childbearing potential, please refer to Women with HIV.
- An alternative regimen is a boosted PI (DRV or LPV) that is active against HIV-2 plus two NRTIs **(BII)**.
- NNRTI-based regimens **are not recommended** for persons with HIV-2 infection **(AII)**.
- Patients with hepatitis B virus (HBV)/HIV-2 coinfection require ART regimens that contain drugs with activity against both HIV-2 and HBV **(AIII)**. See Hepatitis B Virus/HIV Coinfection for more information.
- HIV-2 plasma RNA levels, CD4 cell counts, and clinical status should be monitored to assess treatment response, as is recommended for HIV-1 **(AII)**.
- Persons who have HIV-2 RNA levels that are below the limits of detection before they initiate ART should still undergo routine HIV-2 plasma RNA monitoring in addition to CD4 cell count and clinical monitoring. Unlike HIV-1, persons with HIV-2 requires continued CD4 cell count monitoring, as disease progression can occur in the setting of undetectable HIV-2 viral load **(AIII)**.

Persons with HIV-2 who are of childbearing potential require similar considerations when choosing a regimen as those with HIV-1 (see What to Start). There are no data on HIV-2 treatment as prevention; however, both data from studies of people with HIV-1 and data on the natural history of HIV-2 transmission suggest that effective ART likely provides a reduced risk of transmission to sexual partners.

Resistance-associated viral mutations to NRTIs, PIs, and/or INSTIs may develop in persons with HIV-2 while on ART.[35,45,46] Currently, transmitted drug resistance appears to be rare among people with HIV-2.[47,48] In several small studies, twice-daily dosing of DTG was found to have some residual activity as a second-line INSTI in some persons with HIV-2 who had extensive ART experience and RAL resistance.[49-52] Genotypic algorithms that are used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because the pathways and mutational patterns that lead to resistance may differ between the HIV types (see the HIV2EU Algorithm and the Stanford University HIV Drug Resistance Database).[53] In the event of virologic, immunologic, or clinical failure, a new ART regimen should be constructed in consultation with an expert in HIV-2 management.

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Older Patients with HIV (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Considerations When Caring for Older Patients With HIV
• Antiretroviral therapy (ART) is recommended for all patients regardless of CD4 T lymphocyte cell count **(AI)**. ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART. • Adverse drug events from ART and concomitant drugs may occur more frequently in older patients living with HIV than in younger patients with HIV. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older patients should be monitored closely. • Polypharmacy is common in older patients with HIV; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications. • HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older patients with HIV with complex comorbidities. • Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older patient with HIV.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

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

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

HIV Diagnosis and Prevention in the Older Adult

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

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

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

Impact of Age on HIV Disease Progression

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

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

Initiating Antiretroviral Therapy in the Older Patient with HIV

ART is recommended for all individuals with HIV (**AI**; see Initiation of Antiretroviral Therapy section). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population. In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (patients between ages 45 and 65 years).[21] No data support a preference for any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of patient age. The choice of regimen should instead be informed by a comprehensive review of the patient's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an antiretroviral regimen based on an older patient's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older patients with reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix B, Table 10). In addition, ARV regimen selection may be influenced by potential interaction of antiretroviral medications with drugs used concomitantly to manage comorbidities (see Tables 21a-22b). 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 17).

HIV, Aging, and Antiretroviral Therapy

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

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

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

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

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[28] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young participants with normal organ function who do not have HIV (see Tables 21a-22b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be greater in older patients with HIV than in younger patients with HIV.

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

Non-AIDS HIV-Related Complications and Other Comorbidities

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

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

Switching, Interrupting, and Discontinuing Antiretroviral Therapy in Older Patients

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

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

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

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

Conclusion

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

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Substance Use Disorders and HIV (Last updated July 10, 2019; last reviewed July 10, 2019)

Key Considerations and Recommendations
• Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care **(AII)**.
• The most commonly used substances among people with HIV include alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco.
• Health care providers should be nonjudgmental when addressing substance use with their patients **(AIII)**.
• Persons with HIV and SUDs should be screened for additional mental health disorders **(AII)**.
• Persons with HIV and SUDs should be offered evidenced-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment; see Table 13) as part of comprehensive HIV care in HIV clinical settings **(AI)**.
• Ongoing substance use is not a contraindication to antiretroviral therapy (ART) **(AI)**. Persons who use substances can achieve and maintain viral suppression with ART.
• Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors), the potential for drug-drug interactions, and the risk or severity of substance-associated toxicities (e.g., increased hepatotoxicity or an increased risk of overdose).
• Selection of ART regimens for individuals who practice unhealthy substance and alcohol use should take potential adherence barriers, comorbidities which could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug-drug interactions, and possible adverse events associated with the medications into account **(AII)**.
• ART regimens with once-daily dosing of single-tablet regimens, high barriers to resistance, low hepatotoxicity, and low potential for drug-drug interactions are preferred **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Background on Substance Use Disorders among People with HIV

Ending the HIV epidemic requires addressing substance use among people with HIV, which poses a barrier to optimal engagement in the HIV care continuum. Ongoing substance use may prevent an individual from being tested for HIV, initiating antiretroviral therapy (ART), or adhering to ART, and it may increase the frequency of behaviors that put a person at risk for HIV transmission. Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors, needle sharing, and injection of substances), the potential for drug-drug interactions, and the risk or severity of substance-related toxicities (e.g., increased hepatotoxicity and increased risk of overdose). In the United States, the death toll for drug overdose (70,237 deaths in 2017)[1] now far exceeds the death toll for HIV (15,807 deaths in 2016).[2] As the drug overdose epidemic continues to expand, health care providers need to have a basic understanding of how to screen for and treat substance use disorders in persons with HIV in clinical settings.[3]

Substance use exists on a continuum from episodic use to a substance use disorder (SUD) with its concomitant negative consequences. Research on alcohol consumption has defined a threshold at which consumption does not reach a diagnosis of a SUD, but where the level of consumption is nonetheless hazardous to the person. This level of consumption has been defined as "hazardous drinking." A comparable category does not exist for other substances. The prevalence of substance use and SUDs is higher among people with HIV than among the general public,[4] and polysubstance use is common. This section will focus on the most commonly used substances among people with HIV: alcohol, benzodiazepines, cannabinoids, club drugs,[5] opioids, stimulants (cocaine and methamphetamines), and tobacco.

Persons with HIV may use more than one substance and may not be ready to consider reducing the use of substances or seeking treatment for SUDs. Polysubstance use occurs for multiple reasons, including to

improve the euphoria associated with use (e.g., use of cocaine and heroin mixtures called "speedballs") and to reduce the adverse effects of a particular substance (e.g., the use of alcohol or benzodiazepines to reduce the anxiety caused by cocaine use).

Substance Use and Sexual Risk Taking

There is a growing body of literature describing the intersection of substance use and sexual risk taking ("chemsex"). While a precise definition of "chemsex" is lacking, and the various studies have investigated the use of many different substances, this research highlights the impact of substance use on sexual risk behaviors. In these settings, substances may be used to enhance sexual pleasure, decrease inhibitions related to particular sexual acts, and combat low self-esteem. In a retrospective study in a London sexual health clinic, individuals who disclosed substance use (463 of 1,734 patients) had higher odds of acquiring new HIV infection, bacterial sexually transmitted infections (STIs), and/or hepatitis C virus (HCV).[6] A much larger analysis using the European Men Who Have Sex with Men (MSM) Internet Survey, which collected data from 16,065 United Kingdom-based respondents, found that MSM who reported using methamphetamines or gamma-hydroxybutyrate (GHB) during the previous year were more likely to have gonorrhea infection than MSM who did not use these drugs, with odds ratios of 1.92 and 2.23, respectively.[7] These data emphasize the need to screen patients for substance use and STIs in clinical settings.

Screening for Substance Use Disorders

Screening for SUDs should be incorporated into the routine clinical care of all persons with HIV. The following questions can be used to screen for drug or alcohol use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had X or more drinks in a day?" (X is five for men and four for women).[8] Data are lacking on the appropriate threshold for alcohol use among transgender individuals, so until data clarifies the risks, providers should use the more conservative threshold of four drinks. Individuals with liver disease, including active HCV infection, should not consume alcohol. A positive response of at least one time on either screen should prompt additional screening with other short, yet effective screening tools (see the Screening and Assessment Tools Chart from the National Institute on Drug Abuse). These tools can identify substance use and guide decisions on appropriate treatment interventions. There is currently not enough data to determine how often patients should be screened for SUDs; however, given the potential negative impact that SUDs may have on persons with HIV, it is advisable to ask these questions during every clinical visit.

Health care providers should be nonjudgmental when discussing substance use with their patients. Patients who experience stigma or who feel judged may not trust the health care provider's recommendations, may avoid returning to see that provider again, and may consequently have poorer health outcomes.[9] Language is one way in which stigma is communicated, and words such as "addict" and "dirty urine" convey a negative connotation. The Office of National Drug Control Policy (ONDCP), the American Medical Association, the American Society of Addiction Medicine, the International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, non-stigmatizing language for substance use as described in the "Changing the Language of Addiction" report from ONDCP.

Co-Occurring Mental Illness

Many people who use substances have co-occurring mental health disorders, including a history of trauma that may drive and/or exacerbate their substance use. Conversely, ongoing use of substances can place individuals at risk of trauma, such as sexual assault and sexual exploitation, which may further exacerbate their substance use.[6,10] People with SUDs should undergo evaluation and treatment for concurrent mental health disorders using standardized screening instruments (e.g., the Patient Health Questionnaire-2 [PHQ-2] for depression).[11] Where applicable, clinicians should use available behavioral and pharmacological interventions to address mental health concerns, because recommending that patients stop their substance use without providing treatment for underlying mental health conditions has very limited efficacy.[11]

Several behavioral interventions have shown promise in randomized trials. Motivational interviewing, cognitive behavioral therapy, or a combination of the two have led to decreases in stimulant use, decreases in risky sexual behaviors, and improved adherence to ART.[12] Contingency management, a behavioral intervention that provides rewards for abstinence, has been shown to be effective in decreasing stimulant use among persons with HIV, but the sustained effects of this intervention are less clear.[13]

Selecting and Initiating an Antiretroviral Therapy Regimen

Ongoing substance use is not a contraindication to prescribing ART. Indeed, ART reduces the risk of HIV transmission to sexual and drug-using partners. These clinical, community, and individual benefits should encourage health care providers to initiate ART in people with HIV who use substances, and for those with SUDs.

When selecting ART regimens for individuals who use substances, clinicians should consider potential barriers to adherence (see Adherence to the Continuum of Care), co-morbidities that could impact care (e.g., advanced liver disease from alcohol or HCV), potential drug-drug interactions, and possible adverse events that are associated with the medications. Providers should discuss adherence with their patients during multiple, nonjudgmental evaluations. In general, the use of simplified ART regimens should be considered to aid ART adherence. Regimens for people with SUDs should be easy to take, such as a once-daily, single-tablet regimen,[14] and have a high barrier to resistance or a low risk of hepatotoxicity. Adherence counseling should highlight the benefits of ART use, irrespective of concurrent substance use. Additionally, a reduction in substance use may improve adherence to ART.[15]

Commonly Used Substances and Their Impact on HIV and Antiretroviral Therapy

Health care providers should have a basic understanding of evidence-based treatments for SUDs, including alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The sections below discuss the impact of these substances on persons with HIV and how these substances affect ART use.

Alcohol

Epidemiology

Alcohol consumption is common among persons with HIV. Recent estimates indicate that >50% of persons with HIV in the United States consume any amount of alcohol (with a range of 54% to 67%).[16,17] Among a sample of persons with HIV across seven university-based HIV clinics in the United States, 27% of people screened positive for unhealthy alcohol use as determined by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C).[17] Unhealthy alcohol use includes a spectrum of consumption, including risky or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[18]

Risk-Taking Behaviors, the HIV Care Continuum, and Comorbidities

Unhealthy alcohol use has been linked to HIV acquisition, as unhealthy alcohol use can increase the frequency of behaviors that put a person at risk for sexual transmission of HIV.[19-21] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts were all associated with condomless sex among persons with HIV.[20]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[22,23] Studies have demonstrated both temporal and dose-related relationships between alcohol use and adherence, where ART is more likely to be missed on a given drinking day and the day after drinking, with a stronger association on heavy (binge) drinking days.[24-26] The negative impact of unhealthy alcohol use on ART adherence is likely multifactorial and driven by the effects of intoxication, ART regimen complexity, and patient perceptions of adverse interactions between alcohol and ART drugs.[27-29] Studies have also demonstrated an association between unhealthy alcohol use

and the loss of durable viral suppression,[30,31] greater time spent with a viral load >1,500 copies/mL after ART initiation,[32] increased risk of viral rebound, lower retention in care,[33,34] and increased mortality.[35-37] Unhealthy alcohol use alone (hazardous or AUD) and in combination with other common comorbidities, including viral hepatitis coinfection, can hasten liver fibrosis progression in persons with HIV.[38,39] Finally, in general medical populations, unhealthy alcohol use complicates the management of diabetes mellitus, hypertension, mental health disorders, other substance use, and other chronic diseases and increases the risk for pneumonia, osteoporosis, a number of cancers (e.g., liver, head and neck, and breast cancers), and tuberculosis.

Management of Unhealthy Alcohol Use

On-going alcohol use is not a contraindication for a person to receive ART. However, treatment for unhealthy alcohol use may further improve HIV treatment outcomes. Behavioral treatments for unhealthy alcohol use among persons with HIV demonstrate a small but significant reduction in alcohol use[40] (see additional resources for alcohol management from the National Institute on Alcohol Abuse and Alcoholism and the American Public Health Association). Pharmacotherapy can also reduce alcohol use among persons with HIV. There are three Food and Drug Administration (FDA)-approved pharmacotherapies for AUD: naltrexone, disulfiram, and acamprosate (see Table 13).

Clinical trials have demonstrated the efficacy of naltrexone in reducing the number of heavy drinking days among those with HIV and among the general population. Naltrexone appears to be safe to use in persons with HIV,[41,42] and it is not associated with significant drug-drug interactions or irreversible hepatotoxicity. However, it is not recommended for individuals with decompensated liver disease and should be used with caution in individuals with elevated transaminase levels. Use of naltrexone in persons with HIV and AUD can improve HIV treatment outcomes. In a randomized placebo-controlled trial of 100 prisoners with HIV who met the criteria for AUD, individuals who were provided depot naltrexone upon release from prison were more likely to achieve viral suppression at 6 months than the placebo group (56.7% vs. 30.3%).[42]

Data on the use of disulfiram and acamprosate among persons with HIV are lacking. Notably, integrating treatment for AUD with treatment for HIV has been shown to increase the number of patients who receive alcohol treatment medication, counselling, and formal outpatient alcohol treatment services. Integrating these treatments may also improve the likelihood that a patient will achieve viral suppression on ART. A randomized controlled trial of 128 individuals with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veteran's Administration HIV clinics to treatment as usual. At end of treatment (24 weeks), integrated stepped care resulted in more participants receiving pharmacotherapy for AUD and participating in counseling. Though differences in alcohol use and viral suppression were not seen at 24 weeks, at 52 weeks integrated stepped care was significantly associated with an increased number of alcohol abstinent days, a decrease in the number of drinks per drinking day, and a decreased number of heavy drinking episodes. In addition, the patients in the stepped care group had increased odds of achieving viral suppression (odds ratio [OR] 5.58; 95% confidence interval [CI], 1.11–27.99).[43]

Liver cirrhosis, whether related to chronic heavy alcohol use, viral hepatitis, or nonalcoholic fatty liver disease, can result in altered metabolism of antiretroviral (ARV) drugs. For those who have hepatic impairment due to alcohol-related liver disease, ART dosing should follow the recommendations in Appendix B, Table 10, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

While specific epidemiologic data on the prevalence of benzodiazepine use among persons with HIV are limited, the use of benzodiazepines can impact both morbidity and mortality. Benzodiazepines cause anterograde amnesia, defined as difficulty recalling events after taking the medication. Individuals do not develop tolerance to this neurocognitive effect, and long-term use of benzodiazepines may result in impairment of neurocognitive functioning.[44]

Risk-Taking Behaviors and the HIV Care Continuum

People who inject drugs and who also use benzodiazepines engage in riskier behaviors than the people who inject drugs but who do not use benzodiazepines; these behaviors may include paying for sex, sharing injection equipment with more people, and performing more frequent injections.[45] A cohort of 2,802 people who injected drugs was followed from 1996 to 2013. During that time, benzodiazepines were the substances with the greatest association with mortality.[46] The long-term neurocognitive impact of benzodiazepines on ART adherence among persons with HIV is unclear, but prescribing a memory-impairing medication to persons with HIV who are prone to neurocognitive impairments from other causes increases the risk of poor ART adherence.[47] Benzodiazepines are also used illicitly to counteract the negative side effects of stimulants such as cocaine and methamphetamine.[48]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiologic dependence and life-threatening withdrawal in some patients. When feasible, individuals who chronically take benzodiazepines should be slowly tapered off the benzodiazepines under the supervision of an experienced clinician. Different benzodiazepines have different potencies (e.g., alprazolam is more potent than diazepam) and therefore require different tapers in terms of length and graduated decrease in dosage.

Benzodiazepine and Antiretroviral Drug Interactions

Several pharmacological interactions with ARV drugs have also been described. For example, some benzodiazepines are cytochrome P (CYP) 3A4 substrates; thus, when these benzodiazepines are used with a ritonavir-boosted or cobicistat-boosted ARV drug, their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See Drug-Drug Interactions for available data on benzodiazepine-related interactions.[49]

Cannabinoids

Epidemiology

Both medical and recreational cannabis (marijuana) use are prevalent among people with HIV.[50] Cannabis belongs to a class of compounds that activate cannabinoid receptors. This class, known as cannabinoids, also includes synthetic compounds such as K2. In recent years, cannabinoids have become more popular. In 2009, two cannabinoids were reported to the National Forensic Laboratory Information System. By 2015, 84 compounds had been reported.[51] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[52]

Risk-Taking Behaviors and the HIV Care Continuum

Cannabis has not been shown to negatively impact adherence to ART or a patient's ability to achieve viral suppression. In one study, among 874 persons with HIV, daily cannabis use did not predict lower odds of ART use or achieving an undetectable HIV RNA level, except when combined with binge drinking.[53] Data from the Multicenter AIDS Cohort Study have supported the idea that marijuana use does not predict problems with adherence to ART or achieving viral suppression.[54] In some cases, however, cannabinoids have been listed as the cause of death in overdoses. While data are lacking among adults with HIV, the nationally representative 2015 Youth Risk Behavior Survey (which includes data from 15,624 adolescent students in grades 9 to 12) found that students who had ever used synthetic cannabinoids engaged in riskier activities, including sex, than students who only used marijuana.[55] While the available data suggest that the use of marijuana in not associated with decreased adherence to ART,[56] data are currently lacking on the impact of synthetic cannabinoids on ART adherence. Finally, with the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these products, which may increase the risk of opioid overdose.

Management of Cannabinoid Use

Due to the aforementioned concerns regarding cannabinoid use—particularly the variety of compounds and neuropsychiatric effects—persons with HIV should be discouraged from using cannabinoids until more data are available. There is no pharmacological treatment for cannabinoid use disorder; however, behavioral health treatment may be effective for some patients.[57-59]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects, or that are used to enhance sexual experiences.[5] The use of multiple club drugs or other drugs simultaneously is common. While these substances are used by many different persons with HIV, the majority of data comes from MSM with HIV. Use of club drugs in this population has been shown to negatively impact HIV treatment.[60] Club drugs include methylenedioxymethamphetamine (MDMA), GHB, ketamine, benzodiazepines (see the benzodiazepine section above), and other drugs that are used to enhance the sexual experience (e.g., mephedrone, inhaled nitrates [poppers], and phosphodiesterase-5 inhibitors [PDE5] for erectile dysfunction). Survey data from users of club drugs have also revealed that efavirenz is purchased by people without HIV for its intoxicating effects.[61]

Risk-Taking Behaviors and the HIV Care Continuum

Club drugs have disinhibitory effects. Using club drugs increases the likelihood that a person will engage in high-risk sexual practices, which can increase the risk of HIV transmission. In addition, these disinhibitory effects can lead to poor ART adherence.[49,60,62]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[63] There are no recommended pharmacotherapies at this time, and the most common strategy for treating patients who use club drugs is to employ the behavioral interventions that are used for other drug use disorders.

Club Drug and Antiretroviral Drug Interactions

MDMA, GHB, ketamine, and methamphetamine all have the potential to interact with ARV drugs because they are metabolized, at least in part, by the CYP450 system.[49,62] Overdoses secondary to interactions between the club drugs (i.e., MDMA or GHB) and protease inhibitor-based ART have been reported.[49] For instance, using PDE5 or ketamine concurrently with potent CYP3A4 inhibitors such as ritonavir or cobicistat can lead to potentiation of the effects of these substances.[60]

Cocaine

See the discussion in the section on stimulants below.

Opioids

Epidemiology

Opioids remain a significant concern for persons with HIV, both for the acquisition of HIV (as recently demonstrated in Scott County, Indiana[64]) and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[65] The appropriate use of opioids while caring for people with HIV and chronic pain is an important component of combating the opioid epidemic, but this subject is beyond the scope of this section. Please refer to additional resources, such as those from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America.[66] To combat the opioid overdose epidemic, health care providers should prescribe naloxone for opioid overdose prevention for all patients who are using opioids beyond the short-term treatment of acute pain.[3]

Risk-Taking Behaviors and the HIV Care Continuum

Many people who use opioids start by using opioid tablets (e.g., oxycodone) that are ingested orally or crushed and sniffed. Once tolerance develops, some individuals move from sniffing the crushed tablets to injecting heroin purchased on the streets. This transition from sniffing to injecting dramatically increases the risk of HIV and HCV infection.

Low-cost heroin is often a mix of heroin and higher potency synthetic opioids, such as fentanyl.[65] Methamphetamines and cocaine have also been combined with fentanyl, but at a lower rate than heroin.[67,68] With the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these as well. In all instances where fentanyl or other high-potency opioids are added to other drugs, the risk of overdose increases.

While treatment for an opioid use disorder can improve HIV treatment outcomes, it is not a prerequisite for treating HIV, as some patients are able to successfully adhere to ART despite ongoing opioid use. Although ART coverage among people with HIV who injected drugs increased from 58% to 71% between 2009 and 2015, additional work is needed to improve ART coverage in this population.[69] Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people who injected drugs were less likely to be retained in care; however, this gap in retention had closed by 2012, and people who injected drugs and noninjectors had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort.[70]

Management of Opioid Use

There are three FDA-approved medications for the treatment of opioid use disorder that can help decrease or eliminate opioid use, reduce the risks of morbidity and mortality that are associated with opioid use, and improve HIV treatment success. These medications, collectively termed medication-assisted treatment (MAT), include buprenorphine, methadone, and naltrexone (see Table 13). Buprenorphine and methadone are opioid agonists (the use of these drugs is termed opioid agonist therapy [OAT]), while naltrexone is an opioid-antagonist or "blocker." Both buprenorphine and naltrexone can be prescribed in the setting of routine HIV clinical care.[71] Prescribing buprenorphine requires specific training and licensure (known as an X-waiver; see the Substance Abuse and Mental Health Services Administration [SAMHSA] website for more information). Methadone must be prescribed through a licensed opioid treatment program (OTP). An OTP directory can also be found on the SAMHSA website.

Use of buprenorphine or methadone can lead to reductions in risky behaviors associated with HIV transmission, psychosocial and medical morbidity related to opioid use disorder, and criminal behaviors. People who are receiving treatment for opioid use are already engaging with the health care system; therefore, they are more likely to initiate treatment for HIV and to be adherent to their ART regimens. Both buprenorphine and methadone are cost-effective interventions at the societal level.[72] Methadone has better retention in SUD treatment than either buprenorphine or naltrexone, and it should be considered for individuals who do not achieve successful outcomes with buprenorphine or naltrexone.[73] Buprenorphine has a lower risk of overdose than methadone. In addition, it can be prescribed in primary care offices. Patients who are taking buprenorphine have significantly better retention in treatment than those who are taking daily oral naltrexone.[74] While several randomized, controlled clinical trials have demonstrated efficacy for naltrexone when treating opioid use disorder, subsequent study results have been disappointing; one meta-analysis revealed that oral naltrexone was equivalent to placebo.[75] To address the adherence challenges with naltrexone, a depot formulation was created for monthly administration. This preparation has the potential to improve adherence; however, studies that compare opioid agonists such as buprenorphine and methadone to depot naltrexone as treatments for opioid use disorder have not been conducted. In a randomized, placebo-controlled trial in persons with both HIV and opioid use disorder, participants who received at least three doses of depot naltrexone prior to discharge from prison achieved longer periods of continuous abstinence

after transitioning from prison to the community than those who received either placebo or two or less doses of depot naltrexone.[42] On the basis of these data, methadone or buprenorphine are generally used as first-line agents for the treatment of opioid use disorder. Depot naltrexone is used as an alternative treatment for people who have recently been released from correctional facilities when other options are not available.

Important pharmacokinetic interactions between these medications (particularly methadone) and certain ARV drugs are listed in Drug-Drug Interactions.

Stimulants

Epidemiology

Cocaine and methamphetamine are powerful stimulants that have been associated with multiple detrimental effects to people with HIV, including accelerated disease progression, poor ART adherence, and lack of viral suppression. Cocaine powder is snorted or injected, while the free-base form (crack) is smoked. Methamphetamines can be taken orally or rectally, injected, or smoked. Cocaine and methamphetamine are commonly used with other substances, including alcohol. Individuals who use stimulants experience a sense of euphoria and may have heightened sexual desire and arousal. This can lead to disinhibited sexual behaviors, increasing the risk of HIV transmission.

The prevalence of stimulant use among people with HIV has been estimated to be 5% to 15% across multiple studies.[76-78] Methamphetamine use is more common among MSM,[79] and increased rates of cocaine use have been observed among ethnic and racial minorities and persons with a history of incarceration.[80]

Risk-Taking Behaviors and the HIV Care Continuum

There are multiple negative health consequences of stimulant use among persons with HIV, including rapid development of dependence and adverse effects on multiple organ systems, particularly the central nervous and cardiovascular systems. Stimulant use is associated with neurocognitive impairment,[81] delirium, seizures, hemorrhagic strokes, and mental health disturbances, including anxiety, psychosis, and paranoia.

Stimulant use may independently lead to HIV disease progression even among persons who are taking ART and who have achieved viral suppression. Research to identify the cellular mechanisms responsible for this is ongoing, but increased viral replication, direct effects on the immune system that lead to declines in CD4 T lymphocyte cell count, enhanced immune activation, and disruption of the blood brain barrier that facilitates HIV entry into the brain have been implicated.[82-85] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence, retention in care, and viral suppression. Lack of viral suppression, combined with the increased likelihood of risky sexual behaviors that occurs under the influence of stimulants, poses a threat to the HIV treatment as prevention paradigm.[86]

Non-opioid substances, including methamphetamines and cocaine, are sometimes combined with fentanyl, which increases the risk of overdose.[67,68]

Management of Stimulant Use

Several pharmacologic and behavioral interventions for stimulant dependence have been investigated, and some trials have included people with HIV. The results of pharmacologic interventions have generally been disappointing. There is no FDA-approved pharmacotherapy for cocaine use disorder at this time, despite research on multiple drug classes, including antidepressants, antipsychotics, anticonvulsants, and dopaminergic medications (e.g., disulfiram).[87,88] Among persons with HIV who use crack and opioids, MAT for opioid use disorder may improve ART adherence and viral suppression.[89,90] There is limited evidence that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone)[91] can reduce methamphetamine use or cravings, yet there is no recommended pharmacotherapy to treat stimulant use disorder in persons with HIV.

Several behavioral interventions have shown promise in randomized trials. People with HIV who received

motivational interviewing sessions, cognitive behavioral therapy, or a combination of the two decreased their stimulant use and improved their adherence to ART, and they were less likely to engage in risky sexual behaviors.[12] Contingency management has been shown to be effective in decreasing stimulant use among persons with HIV, but the sustained effects on the reduction of stimulant use and improvements in ART adherence are less clear.[13,77,92] Technology-based interventions, such as text messaging, may have a role in supporting ART adherence and decreasing methamphetamine use among persons with HIV, but further research is needed.[93] Persons with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[12]

Despite the challenges discussed above, persons with HIV who use stimulants can achieve viral suppression with ART[94] and should be prescribed ART even if stimulant use is ongoing.

Tobacco

Epidemiology

The prevalence of tobacco smoking among persons with HIV in the United States is approximately twice that of the general population (33.6% vs. 16.8%). Prevalence is even higher among specific subgroups, including those who use alcohol and/or other drugs, those who have concurrent mental health disorders, and those of a lower socioeconomic status. While smoking rates are declining overall in the United States, persons with HIV are less likely to quit smoking than people in the general population.[95]

Associated Risks of Tobacco Use and HIV Infection

With respect to substance use and HIV, tobacco smoking is the biggest threat to health-related gains achieved through ART. Among individuals with viral suppression on ART, more years of life may be lost from continued smoking than from HIV infection itself.[96,97] Tobacco smoking among persons with HIV is associated with an increased risk of numerous health conditions, including lung cancer and other smoking-related cancers, cardiovascular disease, and pulmonary disease. In a sample of 17,995 persons with HIV on ART in Europe and North America, individuals who smoked had nearly twice the mortality of those who did not (mortality rate ratio 1.94; 95% CI, 1.56–2.41) with significant mortality attributed to cardiovascular disease and non-AIDS related malignancy.[96] Importantly, tobacco cessation reduces the incidence of cardiovascular disease and smoking-related cancers (though definitive data on lung cancer are not available) and improves quality of life.[98-100]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[101-103] cessation strategies when treating patients with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and the U.S. Preventive Services Task Force). These include (but are not limited to) advising the patient to quit smoking, using the five A's, employing motivational interviewing, and referring the patient to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion, and varenicline) have few clinically significant interactions with ARV drugs and can lead to enormous reductions in morbidity and mortality if the person is able to stop smoking. Nicotine replacement is efficacious;[104] however, bupropion doubles rates of smoking cessation compared with nicotine replacement therapy.[105] Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[105,106] Clinical trials among persons with HIV have found varenicline to be both effective and safe.[101,103] In a recent randomized controlled trial among 179 individuals with HIV who were randomized to receive 12 weeks of behavioral counseling and either varenicline or placebo, varenicline use led to an increase in the percentage of participants who achieved a 7-day abstinence period at 12 weeks (28.1% vs. 12.1%, OR 4.5; 95% CI, 1.83–11.2) and produced higher continuous abstinence between weeks 9 and 12 (23.6% vs. 10%, OR 4.65; 95% CI, 1.71–12.67) compared to placebo.[103] While significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among persons with HIV. Varenicline should be used

in combination with relapse prevention strategies and other measures for long-term tobacco cessation.

Table 13. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction with ARV Drugs	Comments
Alcohol Use Disorder			
Acamprosate	666 mg PO three times a day *or* 333 mg PO three times a day for patients with CrCl 30–50 mL/min	No significant interaction with ARV drugs expected.	**Contraindicated** in patients with CrCl <30 mL/min.
Disulfiram	250 mg PO once daily	Use with caution when prescribing an ARV oral solution that contains ethanol and/or propylene glycol (e.g., FPV, LPV/r, RTV).	Counsel patients regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for alcohol use disorder.
Opioid Use Disorder			
Buprenorphine	Individualize buprenorphine dosing based on a patient's opioid use. The dose range is 4–24 mg sublingually. Dosing is once daily or twice daily.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	Buprenorphine has 90% first pass hepatic metabolism. Verify that the patient is using the appropriate technique for sublingual administration before adjusting the dose, as improper administration will result in poor absorption and low drug levels.
Methadone	Individualize dose. Patients who receive higher doses (>100 mg) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug-Drug Interactions for further recommendations.	QTc prolongation is a concern at higher doses. Methadone can only be prescribed for OUD by a licensed OTP.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Longer time of continuous abstinence in those who received depot formulation naltrexone compared to placebo after transition from prison to community.
Nicotine Use Disorder			
Nicotine Replacement Therapy	There are a wide variety of FDA-approved nicotine replacement products. All formulations are effective.	No significant interaction with ARV drugs expected.	Work with the patient to identify the route of delivery that the patient will use and find most helpful.
Bupropion	Start at 150 mg PO daily for three days, then increase to either 150 mg twice daily or 300 mg once daily (only use formulations that are approved for once daily dosing).	Concentration may be reduced when used with ARV drugs that are CYP2D6 inducers. See Drug-Drug Interactions for further recommendations.	Tobacco quit date should ideally be 1 week after starting therapy.
Varenicline	Titrate dose based on tolerability until desired effect is achieved. The goal is to reach a dose of 1 mg PO twice daily. Requires dose adjustment in patients with CrCl <30 mL/min.	No significant interaction with ARV drugs expected.	Tobacco quit date should ideally be 1 week after starting therapy.

Key: ARV = antiretroviral; CrCl = creatinine clearance; CYP = cytochrome P; FDA = Food and Drug Administration; FPV = fosamprenavir; LPV/r = lopinavir/ritonavir; OUD = opioid use disorder; OTP = opioid treatment program; PO = orally; RTV = ritonavir; SR = sustained release

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Transgender People with HIV (Last updated July 10, 2019; last reviewed July 10, 2019)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all transgender people with HIV to improve their health and to reduce the risk of HIV transmission to sexual partners **(AI)**.
- HIV care services should be provided within a gender-affirmative care model to reduce potential barriers to ART adherence and maximize the likelihood of achieving sustained viral suppression **(AII)**.
- Prior to ART initiation, a pregnancy test should be performed for transgender individuals of childbearing potential **(AIII)**.
- Some antiretroviral (ARV) drugs may have pharmacokinetic interactions with gender-affirming hormone therapy. Clinical effects and hormone levels should be monitored routinely with appropriate titrations of estradiol, testosterone, or androgen blockers, as needed **(AIII)**.
- Gender-affirming hormone therapies are associated with hyperlipidemia, elevated cardiovascular risk, and osteopenia; therefore, clinicians should choose an ART regimen that will not increase the risk of these adverse effects **(AIII)**.

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

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

Introduction

Because transgender and nonbinary people bear a disproportionate burden of HIV, it is important for HIV care providers to be knowledgeable about the specific HIV care needs of these individuals.

Terminology

Transgender people are broadly defined as those whose gender identity differs from their assigned sex at birth.[1,2] The terminology used to define transgender identities continues to evolve over time and across geographical and cultural contexts.[3] The terms cisgender, cis-man, and cis-woman are used to describe persons who identify with their assigned sex at birth. The terms used to describe women who were assigned male at birth include transgender women, trans women, transfeminine individuals, and women of transgender experience. The terms for men who were assigned female at birth include transgender men, trans men, transmasculine individuals, and men of transgender experience. Some individuals identify outside the gender binary of man or woman, using words such as gender nonbinary, genderqueer, and gender nonconforming to describe themselves. Other individuals may not have a fixed sense of their gender and may move back and forth among different gender identities; these individuals are described as gender fluid. Agender persons do not identify with having any gender and can use other terms such as null-gender or neutrois.

Gender affirmation describes processes whereby a person receives social recognition, value, and support for their gender identity and expression.[4] Gender affirmation is often described across several dimensions, including social (e.g., social support and acceptance, use of pronouns, names, or clothing that align with their gender identity), medical (e.g., use of hormones or surgery), legal (e.g., legal name change or changing gender markers on identity documents), and psychological (e.g., the degree of self-acceptance and comfort with their gender identity).[5] Medical gender affirmation has been shown to improve mental health outcomes and measures of well-being in transgender individuals.[6,7]

Epidemiology

National surveys indicate that 1.4 million adults in the United States aged 18 years and older identify as transgender, representing 0.6% of the adult population.[8] It is estimated that almost 2% of high school students identify as transgender.[9,10] National, population-based estimates of the numbers of gender nonbinary people in the United States are not yet available; however, 31% of the 27,715 people who completed the 2015 U.S. Transgender Survey (USTS) identified as gender nonbinary.[11] Meta-regression modeling suggests that the number of people who are willing to report that they are transgender and/or gender nonbinary is

likely to increase in the future.[12]

The most recent estimate of HIV prevalence among transgender people is 14% among transgender women and 2% among transgender men.[13] The highest prevalence is among black (44%) and Hispanic/Latino (26%) transgender women.[13] Not enough data were available to estimate HIV prevalence by race/ethnicity among transgender men. Data on HIV prevalence among nonbinary individuals is scant. Of the nonbinary individuals who completed the 2015 USTS, 0.4% self-reported having HIV, including 1% of participants who were assigned male at birth and 0.2% of participants who were assigned female at birth.[11]

In the first national-level analysis of transgender people with HIV, the National HIV Surveillance system identified 2,351 transgender people with newly diagnosed HIV infection from 2009 to 2014. Eighty-four percent of these individuals were transgender women, 15% were transgender men, and 0.7% reported other gender identities.[14] More than one-half of both transgender women (51%) and men (58%) with newly diagnosed HIV were black/African American. Most of these individuals were aged 25 years to 34 years (35%) or 20 years to 24 years (26%). Almost one-half of transgender people with newly diagnosed HIV resided in the South (44%), and 18% had AIDS at the time of diagnosis.

In 2017, the Ryan White HIV/AIDS Program provided services for 8,811 transgender people, representing 1.8% of Ryan White clients.[15] Of these transgender clients, 7,837 (89%) were transgender women, 853 (10%) were transgender men, and 121 (1%) were transgender with current gender unknown. The majority were black and/or African American (5,081 individuals [57.6%]) or Hispanic/Latino (2,619 individuals [29.7%]).

HIV Care Continuum

Some studies have reported that transgender women living with HIV are less likely than cisgender men to receive antiretroviral therapy (ART), be adherent to ART, and achieve viral suppression.[16-21] Transgender people may experience numerous barriers to successful engagement along the HIV care continuum.[11,22] For example, compared with Ryan White clients overall, transgender clients were significantly less likely to have stable housing (77% vs. 87%), live above the federal poverty level (24% v. 37%), and be virally suppressed (81% v. 86%).[15] Experiences of violence, discrimination, and other trauma[11] are common among transgender people and have been associated with ART failure.[23]

Barriers to HIV Care and Treatment

Transgender people may avoid the health care system due to stigma and past negative experiences (e.g., being called the wrong name or pronoun, being verbally harassed, asked invasive questions about being transgender, or having to educate their providers about transgender people).[11,13,14,24-26]

For many transgender people, gender-affirming therapy (e.g., feminizing hormones) is a greater priority than HIV treatment and care.[27,28]

Concerns about adverse interactions between antiretroviral (ARV) drugs and gender-affirming hormone therapy are common among transgender people.[27] One study found that 40% of transgender women with HIV did not take their ARV drugs as directed due to concerns about drug-drug interactions, yet less than half had discussed this concern with their providers.[29]

Facilitating HIV Care Engagement

Gender Affirmation

Individuals are more likely to engage in HIV care when gender affirmation needs are met.[4,25] A national study of transgender people with HIV found that participants who work with HIV care providers who affirm their gender (e.g., who use their chosen name and pronoun) were more likely to be virally suppressed.[28] Adherence to hormone therapy correlates with adherence to ART.[30,31] However, making access to hormone therapy contingent upon ART adherence is associated with lower likelihood of viral suppression.[28]

Integration of HIV Care with Gender Care

According to research with transgender youth[25] and adults,[27] integrating HIV care with gender care facilitates treatment and is associated with viral suppression. In addition to minimizing the number of provider visits and potentially stressful clinical interactions, care integration makes it easier to discuss concerns about drug-drug interactions between HIV treatment and gender-affirming medications. In instances where integrated care is not feasible, the ART prescriber should refer the patient to an appropriate hormone therapy prescriber. Collaboration between these two care providers may enhance the quality of care.

Peer Navigation

Peer navigation has been found to improve the likelihood of durable viral suppression among key populations, including transgender women.[32] Research with youth and adults suggests that having visible transgender staff in the clinical environment also facilitates engagement in care.[25]

Gender-Affirming Clinical Settings

Providing HIV services within gender-affirming environments should be a priority. Concrete steps that clinicians can take include ensuring that registration forms and electronic medical records are inclusive of transgender and gender nonbinary identities, preferably using a two-step method that records both gender and sex assigned at birth.[33] Individuals should be asked for their chosen name and pronouns, and these should be used consistently when speaking to or about the person, regardless of legal name. Clinicians and staff should avail themselves of resource lists, brochures, and other materials that meet the specific needs of transgender people living with HIV. Integrating hormone therapy with HIV services is the recommended practice and requires that HIV providers become knowledgeable about hormone therapy and other aspects of gender-affirming services. When integration of HIV and transgender services is not possible, patients should be referred to clinicians who are knowledgeable in the field of transgender medicine. Both the World Professional Association for Transgender Health (WPATH) and GLMA: Health Professionals Advancing LGBTQ Equality (previously known as the Gay & Lesbian Medical Association) have provider directories that list endocrinologists, primary care providers, and psychiatrists with expertise working with transgender populations.

Pharmacological Considerations

Hormone Therapy

Hormone therapy is an important aspect of gender-affirming care for many transgender individuals. Hormones facilitate the acquisition of secondary sex characteristics that are associated with the affirmed gender. Several guidelines for hormonal treatment of transgender people have been published, including guidelines from the Endocrine Society[34] and WPATH.[35] Clinical outcomes, potential adverse effects, the patient's treatment goals, and the patient's current hormone levels should be taken into account when determining the appropriate doses of hormone and androgen blockers. A clinician should be aware of the typical doses and routes of administration for all of the hormones and androgen blockers that a patient is taking, whether these medications are prescribed or not. All additional interventions (such as gonadectomy) should be documented. These interventions could potentially increase the risk of ART-related adverse effects on cardiovascular and bone health.

Feminizing regimens that are used by transgender women and others who were assigned male at birth usually include estrogens and androgen blockers. Feminizing regimens result in breast growth, redistribution of body fat, softening of the skin, and a decrease in muscle mass.[32] These regimens do not reduce facial (beard) hair or change the voice. In the United States, oral, parenteral, or transdermal preparations of 17-beta estradiol, or, less often, conjugated estrogens, are the mainstay of gender-affirming medical care for transgender women. Spironolactone, a mineralocorticoid receptor antagonist with anti-androgen properties, is usually used for androgen blockade; alternatives include 5-alpha reductase inhibitors that decrease the production of dihydrotestosterone (e.g., finasteride or dutasteride) or gonadotropin releasing hormone agonists (e.g., goserelin acetate and leuprolide acetate). Cyproterone acetate is a steroidal anti-androgen that is frequently

used outside of the United States. Patients may request progesterone to assist with breast growth; however, this has not been proven to be effective.[33] When using feminizing regimens, the goal is to suppress the testosterone level to <50 ng/dL and reach a serum estradiol level in the physiologic cisgender female range of 100 pg/mL to 200 pg/mL.[34]

Masculinizing regimens for transgender men and others who were assigned female at birth involve parenteral or transdermal testosterone preparations. These regimens are designed to stimulate the growth of facial and body hair, increase muscle mass, and deepen the voice; use of these regimens also results in clitoral enlargement, vaginal atrophy, and amenorrhea.[34] When using masculinizing therapy, the testosterone levels should be kept in the usual cisgender male range of 400 ng/dL to 700 ng/dL.[34]

Hormones and Antiretroviral Therapy

Studies that have examined interactions between exogenous estrogens and ART have predominantly focused on combined oral contraceptive use in cisgender women.[36] The data from these studies have been used to make predictions about the direction and extent of drug-drug interactions (Table 14). However, there are known differences between the pharmacologic characteristics of ethinyl estradiol, which is used in contraceptives, and 17-beta estradiol, which is used for gender affirmation. These differences may influence the accuracy of these predictions for feminizing hormonal regimens.

Table 14. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs (page 1 of 2)

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with the Least Potential to Impact GAHT Drugs	All NRTIs Entry Inhibitors: • IBA • MVC • T-20 Unboosted INSTIs: • BIC • DTG • RAL NNRTIs: • RPV • DOR	None	No dose adjustments necessary. Titrate dose based on desired clinical effects and hormone concentrations.
ARV Drugs that may Increase Concentrations of Some GAHT Drugs	EVG/c All boosted PIs	Dutasteride Finasteride Testosterone	Monitor patient for associated adverse effects; decrease the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.
ARV Drugs that may Decrease Concentrations of GAHT Drugs	PI/r NNRTIs: • EFV • ETR • NVP	Estradiol	Increase the dose of estradiol as needed to achieve the desired clinical effects and hormone concentrations.
	NNRTIs: • EFV • ETR • NVP	Dutasteride Finasteride Testosterone	Increase the doses of GAHT drugs as needed to achieve the desired clinical effects and hormone concentrations.

Table 14. Potential Interactions Between the Drugs Used in Gender-Affirming Hormone Therapy and Antiretroviral Drugs (page 2 of 2)

Potential Effect on GAHT Drugs	ARV Drugs	GAHT Drugs that may be Affected by ARV Drugs	Clinical Recommendations for GAHT
ARV Drugs with an Unclear Effect on GAHT Drugs	EVG/c PI/c	Estradiol	There is the potential for increased or decreased estradiol concentrations. Adjust the dose of estradiol to achieve the desired clinical effects and hormone concentrations.

Note: See Tables 21a, 21b, 21c, 21d, and 21e for additional information regarding drug-drug interactions between ARV drugs and gender-affirming medications.

Key: ARV = antiretroviral; BIC = bictegravir; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GAHT = gender-affirming hormone therapy; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; T-20 = enfuvirtide

Other Hormonal Therapy Considerations

Bone Health

Bone metabolism is influenced by sex hormones. Current recommendations for osteoporosis screening are based on age and sex and have not been studied in transgender populations, which include people who have used hormone therapy and/or undergone removal of their gonads. Studies investigating bone mineral density changes in transgender women have shown inconsistent results, with estrogens being associated with both elevations and declines in bone mineral density.[37-39] In one study, transgender women had high rates of osteopenia even before initiating hormones, possibly due to low levels of physical activity and low vitamin D levels.[37] Transgender men who are receiving testosterone appear to maintain adequate bone mineral density.[40] The risk for osteoporosis increases after gonadectomy, especially if hormone regimens are stopped. Consequently, clinicians should consider early screening in this setting.

When using the FRAX® tool, which requires a sex designation, expert consensus is that assigned birth sex should be used, since transgender people who initiate hormones in early adulthood have generally already achieved peak bone mass.[41] Transgender people with HIV should be screened for osteoporosis using dual energy X-ray absorptiometry by age 50, in accordance with current primary care recommendations.[42]

Since the use of tenofovir disoproxil fumarate (TDF) has been associated with reductions in bone mineral density in people with HIV, TDF should be used with caution in transgender people with risk factors for osteoporosis or in those with established osteoporosis.

Interpretation of Laboratory Values

Interpretation of laboratory results requires special attention when reference ranges vary by sex. The sex listed on laboratory requisition forms typically corresponds with the gender listed on the patient's insurance forms and may not reflect the patient's current anatomical or hormonal configuration. Normal values have not been established for transgender individuals who are receiving gender-affirming hormonal or surgical interventions. Interpretation of laboratory results is dependent on the patient's physiology and the specific test being performed. Feldman et al.[43] recommend the following:

- For transgender people who are not taking hormones and have not had gonadectomy, use the sex assigned at birth.
- For transgender people who have undergone gonadectomy and have been stable on hormone therapy, use their affirmed gender.

- For transgender people who retain natal gonads and who may have been on hormone therapy for shorter periods of time, some laboratory tests may require the use of male reference ranges, while others may require the use of female reference ranges.
- Guidelines from the Center of Excellence for Transgender Health[1] recommend using the limits of normal described in the table below.

Limits of Normal When Interpreting Selected Laboratory Results in Transgender Adults

Laboratory Measures	Transgender Women on Gender-Affirming Hormones		Transgender Men on Gender-Affirming Hormones	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Alkaline Phosphatase	Not defined	Male value	Not defined	Male value
Creatinine	Not defined	Male value	Not defined	Male value
Hemoglobin/Hematocrit	Female value	Male value	Male value[a]	Male value

[a] If the patient is menstruating regularly, consider using the female lower limit of normal.

Providers are encouraged to consult with their local laboratories to obtain hormone level reference ranges for both 'male' and 'female' norms, and then apply the correct range when interpreting results based on the current hormonal sex, rather than the sex on the laboratory form.[1] Reference intervals for transgender people have not been established; therefore, hormone status and clinical judgment must be used to assess abnormal laboratory values.[44]

Renal Concerns

Gender-affirming hormones can affect estimates of glomerular filtration rates (eGFR) that rely on serum creatinine due to changes in muscle mass. In one study, transgender men on testosterone had a mean increase in levels of serum creatinine from 0.73 ± 0.03 mg/dL to 0.87 ± 0.04 mg/dL after 3 months to 6 months of treatment. Transgender women on estrogen had a decrease in mean serum creatinine levels from 0.90 ± 0.03 mg/dL to 0.85 ± 0.03 mg/dL.[45] Creatinine-based eGFR calculations may therefore overestimate GFR in transgender women or underestimate GFR in transgender men on hormones. Therefore, using cystatin C-based eGFR calculations may be preferred for patients with marginal renal function.

Cardiovascular Disease Risk

Transgender individuals may have elevated cardiovascular disease (CVD) risk, due to both traditional risk factors and the risk factors associated with hormone use. Rates of tobacco use are higher among transgender people than in the general population,[46] and transgender women have a higher risk of venous thromboembolism and ischemic stroke, primarily associated with duration of estrogen use.[47] Transgender women on estrogens may show an increase in serum levels of triglycerides and high-density lipoproteins (HDL), with a decrease in levels of low-density lipoproteins (LDL).[48] Exogenous testosterone has been associated with increased levels of LDL and decreased levels of HDL among transgender men.[48] Providers should take into consideration CVD risk when selecting ART regimens and gender-affirming hormone therapy regimens.

Assessment of cardiac risk among transgender people with HIV can be complicated by hormone-induced changes in lipid levels as well as sex-specific variations in homocysteine and high sensitivity C-reactive protein.[49] American Heart Association guidelines recommend using sex-specific calculators to determine cardiovascular risk and guide interventions,[50] and they provide no guidance for transgender people whose assigned sex at birth may differ from their hormonal and/or anatomical sex. The Center of Excellence for Transgender Health recommends that providers use the risk calculator for the sex at birth, affirmed gender, or an average of the two depending on the age at which the patient began using hormones and the total amount of time that a patient has been on hormone therapy.[1]

For transgender people with an elevated CVD risk or a history of CVD events, ARV drugs that are associated with CVD should be avoided whenever possible. See Table 17 for a list of ARV drugs that are associated with an increased risk of CVD. See Table 18 for alternative ARV agents to use in individuals with CVD. In transgender women who have an elevated risk for CVD or who have experienced a CVD event, transdermal estradiol may be the safest option for hormone therapy, as it carries a lower risk of thromboembolism than other routes of administration.[51]

Pregnancy Potential

Important information on contraception, drug-drug interactions between ARV drugs and hormonal therapy drugs, and pregnancy is provided in the Women with HIV section. Much of this information also applies to transgender and nonbinary individuals. Below are specific ART considerations for transgender and nonbinary people with pregnancy potential. Clinicians who care for pregnant patients should also consult the current Perinatal Guidelines for a more in-depth discussion and guidance on managing these patients.

Some transgender individuals use exogenous hormones and/or undergo gonadectomy for gender affirmation. Understanding exactly what interventions someone has undergone and the timeline for these interventions will clarify the patient's potential for pregnancy. Transgender individuals without a uterus (by birth or by hysterectomy) do not have pregnancy potential. For transgender people who retain a uterus and ovaries, ovulation may continue in the presence of hormone therapy, and fertility is possible.[1] Gender-affirming surgeries do not impair fertility unless the uterus, ovaries, and vagina are removed.[52,53] All transgender people who have a uterus and ovaries and engage in sexual activity that could result in pregnancy should receive a pregnancy test prior to initiating ART **(AIII)**. All ART-naive persons who are pregnant should be started on ART for their health and to prevent transmission of HIV to the fetus. They should be counseled about ARV drug use during pregnancy, and clinicians should consult the Perinatal Guidelines when designing a regimen **(AIII)**. Unless there are no alternative options, dolutegravir **should not be prescribed** for individuals 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 **(AII)**.

Testosterone Exposure in Transgender Persons with Ovaries

Testosterone alone is not a reliable form of contraception, and pregnancies have been reported in transgender men following prolonged testosterone treatment. Testosterone is a teratogen, and it is contraindicated in pregnancy. Clinicians should assess the reproductive desires and fertility potential of their transgender patients and provide accurate information on contraceptive and reproductive options.[54]

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

Panel's Recommendations

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

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

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

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

Sex Difference Considerations in Antiretroviral Therapy

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

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

Adverse Effects

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

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

Adults and Adolescents with HIV Who Are of Childbearing Potential

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

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

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

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

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

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

Reproductive Options for Serodiscordant Couples

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

Hormonal Contraception

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

Drug-Drug Interactions

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

- **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 21a, 21b, and 21d), which potentially decreases contraceptive efficacy or increases the risk of estrogen- or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[30] Several regimens that include a cobicistat-boosted PI, PI/r, and EVG/c decrease oral contraceptive estradiol levels.[31-34] One PK study showed that DTG did not affect ethinyl estradiol or norgestimate levels.[35] Several studies have shown that use of etravirine, rilpivirine, and NVP did not significantly affect estradiol or progestin levels in individuals with HIV using COCs.[36-38]
- **Injectable Contraceptives:** Small studies of women with HIV who were receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, lopinavir/ritonavir (LPV/r), NVP, nelfinavir (NFV), or NRTI drugs.[39-42]
- **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.[43,44] Studies of women with levonorgestrel- and etonogestrel-releasing implants reported that participants receiving EFV-based ART had decreased bioavailability of levonorgestrel and

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

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARV drugs should not prevent clinicians from prescribing hormonal contraceptives for individuals on ART who prefer this contraceptive method. However, an alternative or additional effective contraceptive method is recommended when there are significant drug interactions between hormonal contraceptives and ARV drugs (see drug interaction Tables 21a, 21b, and 21d and the Perinatal Guidelines).

Risk of HIV Acquisition and Transmission

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

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

Pregnancy

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

Prevention of Perinatal Transmission of HIV

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

Antiretroviral Regimen Considerations

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

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

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

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

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

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

Postpartum Management

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

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

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Considerations for Antiretroviral Use in Patients with Coinfections

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

Panel's Recommendations

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

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

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

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

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

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

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

Recommendations for Patients with HBV/HIV Coinfection

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

Antiretroviral Drugs with Dual Activities against HBV and HIV

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

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

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

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

Recommended Therapy

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

Alternative Therapy

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

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

HBV Drugs Not Recommended

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

Changing Antiretroviral Therapy

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

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

Panel's Recommendations

- All people with HIV should be screened for hepatitis C virus (HCV) infection **(AIII)**. Patients at high risk of HCV infection should be screened annually and whenever incident HCV infection is suspected **(AIII)**.
- Antiretroviral therapy (ART) may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most persons with HCV/HIV coinfection, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 T lymphocyte cell count **(AI)**.
- Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug-drug interactions and overlapping toxicities **(AIII)** (see discussion in the text below and in Table 15).
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy, which includes having their liver fibrosis stage assessed to inform the length of their therapy and subsequent risk of hepatocellular carcinoma and liver disease complications **(AIII)**.
- Persons with chronic HCV/HIV coinfection should be screened for active and prior hepatitis B virus (HBV) infection by testing for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface (HBsAb) and core (HBcAb; total or IgG). Persons who are not immune to HBV infection (HBsAb negative) should receive anti-HBV vaccination **(AIII)**.
- HBV reactivation has been observed in persons with HBV infection during HCV treatment with direct-acting antivirals (DAAs). Accordingly, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy **(AIII)**.

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

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

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

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

Assessment of HCV/HIV Coinfection

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

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

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

Antiretroviral Therapy in HCV/HIV Coinfection

When to Start Antiretroviral Therapy

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

Considerations When Starting Antiretroviral Therapy

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

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions with the HCV treatment regimen (see Table 15).
- In persons with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs.[16,17] Therefore, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes agents with anti-HBV activity (such as tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide plus emtricitabine or lamivudine) prior to initiating HCV therapy **(AIII)**.
- Cirrhotic patients should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and considered for liver transplantation. Furthermore, hepatically metabolized ARV and HCV DAA drugs may be contraindicated or require dose modification in patients with Child-Pugh class B and C disease (see Appendix B, Table 10).

Hepatotoxicity

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

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

Concurrent Treatment of HIV and HCV Infections

Guidance on the treatment and management of HCV in adults with and without HIV can be found in the HCV Guidance. Several ARV drugs and HCV DAAs have the potential for clinically significant pharmacokinetic drug-drug interactions when used in combination. Prior to starting HCV therapy, the ART regimen may need to be modified to reduce the drug-drug interaction potential. Table 15 below provides recommendations on the concomitant use of selected drugs for 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 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 1 of 4)

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

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

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

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 2 of 4)

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

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 3 of 4)

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

Table 15. Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV (page 4 of 4)

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

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

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

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

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

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

Key to Symbols:

✓ = ARV agents that can be used concomitantly

✘ = ARV agents not recommended

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

↑ = increase

↓ = decrease

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

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Tuberculosis/HIV Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

- Selection of a tuberculosis (TB)-preventive treatment for individuals living with HIV and coinfected with latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:
  - Any ART regimen can be used when isoniazid alone is used for LTBI treatment **(AII)**.
  - Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine **(AIII)**.
  - If rifampin or rifabutin is used to treat LTBI, clinicians should review Tables 21a through 21e to assess the potential for interactions among different antiretroviral (ARV) drugs and the rifamycins **(BIII)**.
- All patients with both HIV and active TB who are not on ART should be started on ART as described below:
  - **In patients with CD4 counts <50 cells/mm^3:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.
  - **In patients with CD4 counts ≥50 cells/mm^3:** Initiate ART within 8 weeks of starting TB treatment **(AIII)**.
  - **In all pregnant women with HIV:** Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV **(AIII)**.
  - **In patients with tuberculous meningitis:** Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial **(AI)**.
- Rifamycins are critical components of TB treatment regimens and should be included for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycins have a considerable potential for drug-drug interactions. Clinicians should review Tables 21a through 21e to assess the potential for interactions among different ARV drugs and the rifamycins **(BIII)**.

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

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

Management of Latent Tuberculosis Infection in HIV-Infected Patients

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

Anti-Tuberculosis Therapy as Preventive Tuberculosis Treatment

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

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

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

can potentially cause significant drug-drug interactions, there are now pharmacokinetic (PK) data supporting its use with efavirenz (EFV)[6] and raltegravir (RAL)[7] **(AIII)**. Rifampin or rifabutin for 4 months may also be considered for LTBI treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 21a through 21e).

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

Antiretroviral Therapy's Effect in Preventing Active Tuberculosis

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

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

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

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

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

Tuberculosis Diagnosed While Patient is Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the ARV regimen should be assessed with particular attention to potential PK interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 21a through 21e for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

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

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

Patients with CD4 count <50 cells/mm^3: Three large randomized clinical trials in patients with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm^3 significantly reduced AIDS events or deaths.[11-14] In these studies, early ART was defined as starting ART within 2 weeks and at no later than 4 weeks after initiation of TB therapy. In all three studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm^3 **(AI)**.

Patients with CD4 counts ≥50 cells/mm^3: In the three studies mentioned above, there was no survival benefit for patients with CD4 count ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality in the SAPiT-1 study.[11] Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in patients with TB and CD4 counts over 50 cells/mm^3. However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the the Panel recommends ART initiation within 8 weeks of starting TB treatment for those with ≥50 cells/mm^3 **(AIII)**.

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

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

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

Drug Interaction Considerations

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

transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs) elvitegravir (EVG) and the CCR5 antagonist maraviroc (MVC). Additionally, UGT1A1 induction may hasten the metabolism of the INSTIs dolutegravir (DTG) and RAL. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and the fusion inhibitor enfuvirtide are not expected to have significant drug interactions with the rifamycins. As a P-gp substrate, tenofovir alafenamide (TAF)'s drug exposure may be reduced by rifamycins; therefore, concomitant administration of TAF and a rifamycin is not recommended at this time.[20] Tables 21a through 21e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly.

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

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 21a through 21e for dosing recommendations).

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

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

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

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

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

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

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

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Limitations to Treatment Safety and Efficacy

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

Key Summary of Adherence to the Continuum of Care

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

Introduction

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

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

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

Linkage to Care

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

Monitoring Linkage to Care

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

Improving Linkage to Care

Strategies to improve linkage to care are summarized in Table 16. Linkage efforts should include immediate referral to care at diagnosis, appointment reminders, and outreach efforts if needed.[13] The only intervention shown to increase linkage to care in a randomized trial conducted in the United States is the Anti-Retroviral Treatment and Access to Services (ARTAS) intervention.[14] ARTAS is a strength-based intervention which aims to facilitate linkage to and retention in care for persons with recently diagnosed HIV. The ARTAS intervention was tested in four cities and enrolled a diverse group of persons. The participants in the ARTAS intervention trial were randomized to either an intervention arm or a control arm. Participants randomized to the control arm received information about HIV and care resources and a referral to a local HIV Medical provider. Each participant in the intervention arm worked with an ARTAS interventionist for five sessions, 90 days, or until linkage—whichever came first. The interventionist helped the participant to identify and use his or her strengths, abilities, and skills to link to HIV care, and linked the participant to community resources. Linkage to care, defined as completing at least one visit with an HIV clinician within the first 6 months, was greater among the ARTAS participants than the control participants (78% vs. 60%, adjusted RR = 1.36, $P < 0.001$). Furthermore, a greater percentage of ARTAS participants were retained in care, defined as visiting an HIV clinician at least once in each of the first two 6-month blocks after enrollment (64% vs. 49% for ARTAS and control participants, respectively; adjusted RR = 1.41, $P = 0.006$). ARTAS has been replicated in a community-based study.[15] CDC supports free training in the ARTAS intervention (https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/PublicHealthStrategies/ARTAS.aspx). Other studies support the importance of post-test counseling to educate, motivate, and present positive messages about

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

Retention in Care

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

Monitoring Retention in Care

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

Improving Retention in Care

Strategies to improve retention in care are summarized in Table 16. The Retention through Enhanced Personal Contact (REPC) intervention was tested in a randomized trial in six clinics in the United States. The intervention relied on personal contact by an interventionist with at-risk patients. It included a brief face-to-face meeting upon returning to care and at each clinic visit and three types of phone calls: to check on patients between visits, as appointment reminders just before visits, and to attempt to reschedule missed visits. REPC resulted in small but significant improvements in retention in care, including in racial/ethnic minority populations and persons with detectable plasma HIV RNA.[31] In-clinic opioid replacement therapy helps opioid users remain in care.[32] An intervention using the electronic medical record to alert providers when patients had suboptimal follow-up or high viral loads also improved retention in care.[33] On the other hand, in two randomized trials involving out-of-care, hospitalized patients with HIV, peer counselors and patient navigators did not improve relinkage to care after hospital discharge.[34,35] Data from nonrandomized studies support:

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

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

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

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

Adherence to Antiretroviral Therapy

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

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

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

Monitoring Adherence to Antiretroviral Therapy

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

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

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

Improving Adherence to Antiretroviral Therapy

Strategies to improve adherence to ART are summarized in Table 16. Just as they support retention in care, all health care team members play integral roles in successful ART adherence programs.[51,54-56] An increasing number of interventions have proven effective in improving adherence to ART (for descriptions of the interventions, see http://www.cdc.gov/hiv/research/interventionresearch/compendium/ma/index.html). The many options can be customized to suit a range of needs and settings.

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

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

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

Conclusion

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

- Regularly assess adherence to ART and appointments.
- Engage a patient who is struggling with adherence at any step on the care continuum with a constructive, collaborative, nonjudgmental, and problem-solving approach rather than reprimanding them or lecturing them on the importance of adherence.
- Elicit an individual's barriers to adherence, which may include personal barriers (e.g., substance use, housing instability, stigma, lack of transportation), clinic barriers (e.g., limited clinic hours, processes that make it more difficult to obtain prescriptions or schedule appointments), and system barriers (e.g., copays, prior approvals, processes that complicate maintaining pharmacy benefits or obtaining refills).
- Tailor approaches to improve adherence to an individual's needs and barriers, for example, by changing ART to simplify dosing or reduce side effects, finding resources to assist with copays or other out-of-pocket costs (see Table 16) to maintain an uninterrupted supply of ART and access to clinicians, or linking patients to counseling to overcome stigma, substance use, or depression.
- Place patients with apparent ART adherence problems on regimens with high genetic barriers to resistance, such as dolutegravir or boosted-darunavir regimens. When selecting the regimen, consider possible side effects, out-of-pocket costs, convenience, and patient preferences since the only regimen that will work is the one the patient can obtain and is willing and able to take.
- Understand that multidisciplinary approaches and time to understand and address barriers are needed in many situations, and that the clinician's role is to help the patient to understand the importance of adherence to the continuum of care and reveal any barriers to adherence, and link the patient to resources to overcome those barriers.

Table 16. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 1 of 2)

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

Table 16. Strategies to Improve Linkage to Care, Retention in Care, Adherence to Appointments, and Adherence to Antiretroviral Therapy (page 2 of 2)

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

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

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

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

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

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

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. Table 17 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 3–9.

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 1 of 5)

"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.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia TPV: Intracranial hemorrhage is associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, and the use of vitamin E supplements.	N/A	N/A
Bone Density Effects	TDF: Associated with greater loss of BMD than other NRTIs. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. TAF: Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	RPV, EFV: QTc prolongation	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.	N/A	N/A
Cardiovascular Disease	ABC and ddI: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	DRV, FPV, IDV, and LPV/r: Associated with cardiovascular events in some cohorts	N/A	N/A
Cholelithiasis	N/A	N/A	ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months.	N/A	N/A

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 2 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Diabetes Mellitus and Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all, PIs.	N/A	N/A
Dyslipidemia	d4T > ZDV > ABC: ↑ TG and LDL TAF: ↑ TG, ↑ LDL, ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	EFV: ↑ TG, ↑ LDL, ↑ HDL	All RTV- or COBI-Boosted PIs: ↑ TG, ↑ LDL, ↑ HDL LPV/r and FPV/r > DRV/r and ATV/r: ↑ TG	EVG/c: ↑ TG, ↑ LDL, ↑ HDL	N/A
Gastrointestinal Effects	ddI and ZDV > Other NRTIs: Nausea and vomiting ddI: Pancreatitis	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) NFV and LPV/r > DRV/r and ATV/r: Diarrhea	EVG/c: Nausea and diarrhea	IBA: 8% of patients reported diarrhea in a study of 40 people.
Hepatic Effects	**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.	EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported; 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	N/A	MVC: Hepatotoxicity with or without rash or HSRs reported.

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 3 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: **Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 9 days; 90% of reactions occur within first 6 weeks of treatment. HSR Symptoms (in Order of Descending Frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	NVP: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: HSR reported as part of a syndrome related to hepatotoxicity.
Lactic Acidosis	Reported with 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 >10 mmol/L. Women and obese patients at increased risk.	N/A	N/A	N/A	N/A
Lipodystrophy	Lipoatrophy: d4T > ZDV. More likely when NRTIs are coadministered with EFV than with an RTV-boosted PI.	Lipohypertrophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 4 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Myopathy/ Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL and DTG: ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A
Nervous System/ Psychiatric Effects	d4T > ddI: Peripheral neuropathy (can be irreversible) d4T: Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	Neuropsychiatric Events: EFV > RPV, DOR > ETR EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risk factors include presence of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide was found in a retrospective analysis of comparative trials. RPV: Depression, suicidality, sleep disturbances DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality/self-harm	N/A	All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, and TPV	All INSTIs	MVC, IBA

Table 17. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (page 5 of 5)

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; 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 = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Switching Antiretroviral 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 18 lists several major ART-associated adverse events and the options for appropriate switches between agents in an ARV regimen. The table focuses on the ARVs most commonly used in the United States and lists substitutions that are supported by ARV switch studies, the findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching agents in 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 18. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	TAF or ABC[b] NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered, if appropriate.	Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.
Bone Marrow Suppression	ZDV	TDF, TAF, or ABC[b]	ZDV has been associated with neutropenia and macrocytic anemia.
Cardiac QTc Interval Prolongation	EFV, RPV	A PI- or INSTI-based regimen	High EFV and RPV exposures may cause QT prolongation. Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.
Cardiovascular Events Myocardial infarction, ischemic stroke	ABC	TDF, TAF, FTC, or 3TC	ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.
	RTV- or COBI-boosted PI regimens, EFV, EVG/c	RAL, DTG, BIC, or RPV	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.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (see Comments column).	In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. 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.
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted regimens, and EFV	RAL, DTG, BIC, or RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]

Table 18. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, BIC, or EVG/c	GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient and do not warrant substitution unless they are persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, BIC, or NNRTIs	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.
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.
	MVC	Suitable alternative ART	
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, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient.
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is associated with prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, 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	ATV/c, ATV/r, or another drug class (e.g., INSTI)	Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.

Table 18. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 3 of 3)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Renal Effects Including proximal renal tubulopathy and elevated creatinine	TDF[a]	ABC,[b] 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	COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by >0.4 mg/dL.
Stones Nephrolithiasis and cholelithiasis	ATV, ATV/c, ATV/r	DRV/c, DRV/r, INSTI, or NNRTI	This switch should be made if the clinician believes ATV is the cause of the stones.

[a] In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.

Key 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

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Cost Considerations and Antiretroviral Therapy (Last updated July 14, 2016; last reviewed July 14, 2016)

Although antiretroviral therapy (ART) is expensive (see Table 19 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 19 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 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 1 of 5)

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 19 includes three benchmark prices, rounded to the nearest dollar, for commonly used antiretroviral (ARV) drugs[a] as a general reference for health care providers when considering the cost of HIV treatment. Health care providers should contact patients' pharmacies or 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.

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir					
• Generic	300 mg tablet	60 tablets	$150 to $482	$579 to $603	$44
• Ziagen	300 mg tablet	60 tablets	$559	$670	
Emtricitabine					
• Emtriva	200 mg capsules	30 capsules	$537	$644	N/A
Lamivudine					
• Generic	300 mg tablet	30 tablets	$75 to $343	$429 to $430	$83
• Epivir	300 mg tablet	30 tablets	$416	$499	

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 2 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Nucleoside Reverse Transcriptase Inhibitors (NRTIs), continued					
Tenofovir Disoproxil Fumarate					
• Generic	300 mg tablet	30 tablets	$58 to $922	$110 to $1,216	Pending
• Viread	300 mg tablet	30 tablets	$1,140	$1,368	
Zidovudine					
• Generic	300 mg tablet	60 tablets	$36 to $54	$54 to $365	$13
NRTI Combination Products					
Abacavir/Lamivudine					
• Generic	600 mg/300 mg tablets	30 tablets	$185 to $1,116	$1,395	$356
• Epzicom	600 mg/300 mg tablets	30 tablets	$1,292	$1,550	
Tenofovir Alafenamide/Emtricitabine					
• Descovy	25 mg/200 mg tablet	30 tablets	$1,676	$2,011	N/A
Tenofovir Disoproxil Fumarate/Emtricitabine					
• Truvada	300 mg/200 mg tablet	30 tablets	$1,676	$2,011	N/A
Tenofovir Disoproxil Fumarate/Lamivudine					
• Cimduo	300 mg/300 mg tablet	30 tablets	$1,005	$1,207	N/A
Zidovudine/Lamivudine					
• Generic	300 mg/150 mg tablet	60 tablets	$134 to $578	$878 to $932	$47
• Combivir	300 mg/150 mg tablet	60 tablets	$901	$1,082	
Abacavir Sulfate/Zidovudine/Lamivudine					
• Generic	300 mg/300 mg/150 mg tablet	60 tablets	$1,391	$1,738	Pending
• Trizivir	300 mg/300 mg/150 mg tablet	60 tablets	$1,610	$1,932	
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Efavirenz					
• Generic	600 mg tablet	30 tablets	$894	$1,118	Pending
• Sustiva	600 mg tablet	30 tablets	$981	$1,177	
Doravirine					
• Pifeltro	100 mg tablet	30 tablets	$1,380	$1,656	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 3 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), continued					
Etravirine					
• Intelence	200 mg tablet	60 tablets	$1,296	$1,523	N/A
Nevirapine					
• Generic	200 mg tablet	60 tablets	$10 to $45	$648 to $651	$37
• Viramune	200 mg tablet	60 tablets	$855	$1,026	
• Generic XR	400 mg tablet	30 tablets	$246 to $565	$678 to $706	$231
• Viramune XR	400 mg tablet	30 tablets	$793	$951	
Rilpivirine					
• Edurant	25 mg tablet	30 tablets	$1043	$1,252	N/A
Protease Inhibitors (PIs)					
Atazanavir					
• Generic	200 mg capsule	60 capsules	$878 to $1,264	$1,580 to $1,668	Pending
• Reyataz	200 mg capsule	60 capsules	$1,463	$1,756	
• Generic	300 mg capsule	30 capsules	$870 to $1,252	$1,565 to $1,652	Pending
• Reyataz	300 mg capsule	30 capsules	$1,449	$1,739	
Atazanavir/Cobicistat					
• Evotaz	300/150 mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
• Prezista	600 mg tablet	60 tablets	$1,581	$1,897	N/A
• Prezista	800 mg tablet	30 tablets	$1,581	$1,897	N/A
• Prezista	100 mg/mL suspension	200 mL	$878	$1,054	N/A
Darunavir/Cobicistat					
• Prezcobix	800 mg/150 mg tablet	30 tablets	$1,806	$2,168	N/A
Lopinavir/Ritonavir					
• Kaletra	200 mg/50 mg tablet	120 tablets	$1,024	$1,229	N/A
Tipranavir					
• Aptivus	250 mg capsule	120 capsules	$1,578	$1,894	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 4 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Integrase Strand Transfer Inhibitors (INSTIs)					
Dolutegravir					
• Tivicay	50 mg tablet	30 tablets	$1,658	$1,989	N/A
• Tivicay	50 mg tablet	60 tablets	$3,315	$3,978	N/A
Raltegravir					
• Isentress	400 mg tablet	60 tablets	$1,500	$1,800	N/A
• Isentress HD	600 mg tablet	60 tablets	$1,500	$1,800	N/A
Fusion Inhibitor					
Enfuvirtide					
• Fuzeon	90 mg injection kit	60 doses (1 kit)	$3,586	$4,303	N/A
CCR5 Antagonist					
Maraviroc					
• Selzentry	150 mg tablet	60 tablets	$1,511	$1,813	N/A
• Selzentry	300 mg tablet	60 tablets	$1,511	$1,813	N/A
• Selzentry	300 mg tablet	120 tablets	$3,022	$3,626	N/A
CD4-Directed Post-Attachment Inhibitor					
Ibalizumab-uiyk					
• Trogarzo	200 mg vials	8 vials	$9,080	$10,896	N/A
Coformulated Combination Products as Single Tablet Regimens					
Bictegravir/Tenofovir Alafenamide/Emtricitabine					
• Biktarvy	50 mg/25 mg/200 mg	30 tablets	$2,946	$3,535	N/A
Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Symtuza	600 mg/150 mg/10 mg/200 mg	30 tablets	$3,482	$4,178	N/A
Dolutegravir/Abacavir/Lamivudine					
• Triumeq	50 mg/600 mg/300 mg tablet	30 tablets	$2,805	$3,366	N/A
Dolutegravir/Rilpivirine					
• Juluca	50 mg/25 mg	30 tablets	$2,579	$3,095	N/A
Doravirine/Tenofovir Disoproxil Fumarate/Lamivudine					
• Delstrigo	100 mg/300 mg/300 mg	30 tablets	$2,100	$2,520	N/A

Table 19. Monthly Average Prices of Commonly Used Antiretroviral Drugs (Last updated November 26, 2018; last reviewed October 25, 2018) (page 5 of 5)

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of 9/1/2018)[c]
Coformulated Combination Products as Single Tablet Regimens, continued					
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Atripla	600 mg/300 mg/200 mg tablet	30 tablets	$2,724	$3,269	N/A
Efavirenz/Tenofovir Disoproxil Fumarate/Lamivudine					
• Symfi	600 mg/300 mg/300 mg tablet	30 tablets	$1,634	$1,961	N/A
• Symfi Lo	400 mg/300 mg/300 mg tablet	30 tablets	$1,634	$1,961	N/A
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine					
• Genvoya	150 mg/150 mg/10 mg/200 mg tablet	30 tablets	$2,946	$3,535	N/A
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine					
• Stribild	150 mg/150 mg/300 mg/200 mg tablet	30 tablets	$3,090	$3,708	N/A
Rilpivirine/Tenofovir Alafenamide/Emtricitabine					
• Odefsey	25 mg/25 mg/200 mg tablet	30 tablets	$2,681	$3,217	N/A
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine					
• Complera	25 mg/300 mg/200 mg tablet	30 tablets	$2,681	$3,217	N/A
Pharmacokinetic Enhancers (Boosters)					
Cobicistat					
• Tybost	150 mg tablet	30 tablets	$219	$264	N/A
Ritonavir					
• Generic	100 mg tablet	30 tablets	$222	$278	Pending
• Norvir	100 mg tablet	30 tablets	$257	$309	

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

[b] Source: IBM Watson Health. Micromedex Red Book [database]. 2018. Available at: https://www.micromedexsolutions.com

[c] Source: Medicare & Medicaid Services. Federal Upper Limits—September 2018 [database]. 2018 September 1. Available at: https://www.medicaid.gov/medicaid/prescription-drugs/pharmacy-pricing/index.html.

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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 20.

Pharmacokinetic Interactions Affecting Drug Absorption

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

- Acid-reducing agents, such as proton pump inhibitors, H2 antagonists, or antacids, can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir [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 21a through 22b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose 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 20. 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.

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
INSTIs								
BIC	N/A	Concentration decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
EVG	N/A		N/A	3A4	N/A	2C9	Substrate	N/A
RAL	N/A		N/A	N/A	N/A	N/A	Substrate	N/A
PK Enhancers (Boosters)								
COBI	N/A	N/A	Inhibitor	3A4	3A4, 2D6	N/A	N/A	N/A
RTV	N/A	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer	N/A
PIs **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
ATV	Concentration decreased	N/A	Substrate, inducer, inhibitor	3A4	3A4	N/A	Inhibitor	OATP inhibitor
DRV	N/A	N/A	Substrate, inducer	3A4	3A4	2C9	N/A	OATP inhibitor
FPV	Concentration decreased by H2 antagonist	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	N/A
LPV	N/A	N/A	Substrate	3A4	3A4	N/A	N/A	OATP inhibitor
SQV	N/A	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	OATP inhibitor
TPV	N/A	N/A	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	N/A	OATP inhibitor
NNRTIs								
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A	N/A

Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
NNRTIs, continued								
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A	N/A
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A	N/A
RPV	Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A	N/A
NRTIs								
ABC	N/A	N/A	N/A	N/A	N/A	N/A	Substrate	Alcohol dehydrogenase substrate
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	OATP substrate
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	Competition of active renal tubular secretion
ZDV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Glucuronidation
CCR5 Antagonist								
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A	N/A
Fusion Inhibitor								
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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 21a. 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 21c, 22a, and 22b.

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

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.

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	All PIs	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	All PIs	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	All PIs	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	All PIs	↔ or ↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	All PIs	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1–2 hours after antacids or buffered medications.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H2 Receptor Antagonists	ATV (unboosted)	↓ ATV	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.
	ATV/c, ATV/r	↓ ATV	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).
	DRV/c, DRV/r, LPV/r	↔ demonstrated or expected	No dose adjustment necessary.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 19)

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. PPIs should be administered at least 12 hours before ATV/c or ATV/r. **PPIs are not recommended in PI-experienced patients.**
	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.
	DRV/c, DRV/r	↔ betrixaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
Dabigatran	ATV/c, ATV/r, LPV/r	↑ dabigatran expected With COBI 150 mg Alone: • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran dosing instructions for concomitant use with P-gp inhibitors in dabigatran prescribing information.
	DRV/c, DRV/r	↔ dabigatran expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
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
	DRV/c, DRV/r	↔ edoxaban expected	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations available at this time. Consider alternative ARV or warfarin.
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 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Warfarin	PI/r	↓ warfarin possible	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.
	PI/c	No data	
Anticonvulsants			
Carbamazepine	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ARV.
	ATV/r, LPV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	Carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PI/c	↑ carbamazepine possible ↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Eslicarbazepine, Oxcarbazepine	All PIs	↓ PI possible	Consider alternative anticonvulsant or ARV. If coadministration is necessary, monitor for virologic response. Consider monitoring anticonvulsant and PI concentration.
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
Lamotrigine	ATV (unboosted)	Lamotrigine: no effect	No dose adjustment necessary.
	ATV/r	Lamotrigine AUC ↓ 32%	A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant.
	LPV/r	Lamotrigine AUC ↓ 50% LPV: no significant change	
	DRV/r, TPV/r	↓ lamotrigine possible	
	PI/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Phenobarbital	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
	ATV (unboosted), PI/r	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily or unboosted ATV.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Phenytoin	ATV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r.
	ATV/r, DRV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	LPV/r	Phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PI/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated.**
Valproic Acid (VPA)	PI/c, PI/r	↓ or ↔VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below)			
Aripiprazole	PI/c, PI/r	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate dose 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.
	ATV (unboosted)	↑ aripiprazole expected	Administer 50% of the usual aripiprazole dose. Titrate 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.
Brexpiprazole	PI/c, PI/r	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate 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. Titrate 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%	Titrate bupropion dose based on clinical response.
	TPV/r	Bupropion AUC ↓ 46%	
	ATV/r, DRV/r	↓ bupropion possible	
	PI/c	↔ bupropion expected	No dose adjustment necessary.
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, and Antipsychotics (also see Sedative/Hypnotics section below), continued			
Cariprazine	All PIs	↑ cariprazine expected	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. 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.
Fluvoxamine	All PIs	↑ fluvoxamine possible	Titrate fluvoxamine dose based on clinical response.
Lurasidone	PI/c, PI/r	↑ lurasidone expected	**Contraindicated.**
	ATV (unboosted)	↑ lurasidone expected	Consider alternative therapy. If coadministration is necessary, reduce lurasidone dose by 50%.
Pimavanserin	All PIs	↑ pimavanserin expected	Reduce dose from pimavanserin 34 mg daily to pimavanserin 17 mg daily.
Pimozide	All PIs	↑ pimozide expected	**Contraindicated.**
Quetiapine	All PIs	↑ quetiapine expected	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. 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.
Trazodone	All PIs	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and CV adverse effects.
Tricyclic Antidepressants (TCA) Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	All PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Other Antipsychotics (CYP3A4 and/or CYP2D6 substrates)	PI/c, PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	DRV/r	Paroxetine AUC ↓ 39% Sertraline AUC ↓ 49%	Titrate SSRI dose based on clinical response.
	ATV/r, LPV/r, TPV/r	No data	
	PI/c	Effects unknown	Titrate SSRI dose using the lowest available initial or maintenance dose.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	PI/c, ATV/r, DRV/r, LPV/r	No significant effect observed or expected	No dose adjustment necessary.
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV.
Isavuconazole	LPV/r	Isavuconazole AUC ↑ 96% LPV AUC ↓ 27% RTV AUC ↓ 31%	If coadministered, consider monitoring isavuconazole concentrations and toxicities and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations and toxicities. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dose adjustments. Doses >200 mg/day **are not recommended** with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels.
Posaconazole	ATV/r	ATV AUC ↑ 146% ↑ posaconazole possible	If coadministered, monitor for PI adverse effects. Consider monitoring for posaconazole concentrations and toxicities.
	ATV	ATV AUC ↑ 268% ↑ posaconazole possible	
	ATV/c, DRV/c, DRV/r, LPV/r, TPV/r	↑ PI possible ↑ posaconazole possible	
Voriconazole	ATV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	RTV 100 mg BID ↓ voriconazole AUC 39%	Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk. If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly.
	PI/c	Effect on voriconazole unknown	
Antihyperglycemics			
Canagliflozin	PI/r	↓ canagliflozin expected	If a patient is already tolerating canagliflozin 100 mg daily, has an eGFR >60 mL/min/1.73m^2, and requires additional glycemic control, consider increasing dose to canagliflozin 300 mg daily.
	PI/c	↓ canagliflozin possible	If used in combination, monitor glycemic control.
Saxagliptin	All PIs	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily
Dapagliflozin/ Saxagliptin	All PIs	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimalarials			
Artemether/ Lumefantrine	DRV/r	Artemether AUC ↓ 16% DHA[a] AUC ↓ 18% Lumefantrine AUC ↑ 2.5-fold	Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity.
	DRV/c	↑ lumefantrine expected Effect on artemether unknown	
	LPV/r	Artemether AUC ↓ 40% DHA AUC ↓ 17% Lumefantrine AUC ↑ 470%	

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials, continued			
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_{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%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	All PIs	↑ clarithromycin expected DRV/r ↑ clarithromycin AUC 57% LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% TPV/r ↑ clarithromycin 19% Clarithromycin ↑ TPV 66%	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 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and nontuberculosis mycobacterial infections), continued			
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	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.
	ATV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Once Daily) plus ATV/r: • Rifabutin AUC ↑ 110% and metabolite AUC ↑ 2,101%	
	DRV/r	Compared with Rifabutin (300 mg Once Daily) Alone, Rifabutin (150 mg Every Other Day) plus DRV/r: • Rifabutin AUC ↔ and metabolite AUC ↑ 881%	
	LPV/r	Compared with Rifabutin (300 mg daily) Alone, Rifabutin (150 mg Once Daily) plus LPV/r: • Rifabutin AUC ↑ 203% and metabolite AUC ↑ 375%	
	TPV/r	Rifabutin AUC ↑ 190% and metabolite AUC ↑ 1,971%	
	PI/c	↑ rifabutin expected	
Rifampin	All PIs	↓ PI concentration by >75%	**Contraindicated.** Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister.**
Antipneumocystis and Antitoxoplasmosis Drug			
Atovaquone	ATV/r	↔ atovaquone	No dose adjustment necessary.
Cardiac Medications			
Amiodarone	TPV/r	↑ both amiodarone and PI possible	**Contraindicated.**
	All PIs except TPV/r	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug levels.
Antiarrhythmics (e.g., disopyramide, dofetilide, lidocaine, mexiletine, propafenone)	ATV (unboosted)	↑ antiarrhythmic possible	Consider alternative antiarrhythmics or ARV. If coadministered, monitor for antiarrhythmic toxicities.
	PI/c, PI/r	↑ antiarrhythmic possible	**Do not coadminister.** Consider alternative antiarrhythmics or ARV.
Dronedarone	ATV (unboosted)	↑ dronedarone possible	**Do not coadminister.**
	PI/c, PI/r	↑ dronedarone expected	**Contraindicated.**
Flecanide	All PIs except TPV/r	↑ flecainide possible	**Do not coadminister.**
	TPV/r	↑ flecanide expected	**Contraindicated.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 19)

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

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	DRV/r	↔ 17-BMP (active metabolite) AUC RTV 100 mg BID ↑ 17-BMP AUC 2-fold	No dose adjustment necessary.
	All PIs except DRV/r	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	All PIs	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold	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 adverse effects associated with corticosteroids.** Consider an alternative corticosteroid (e.g., beclomethasone).
Betamethasone, Budesonide Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic corticosteroid outweigh the risks of adverse effects associated with systemic corticosteroids.**
Dexamethasone Systemic	All PIs	↑ glucocorticoids possible ↓ PI possible	Consider alternative corticosteroid for long-term use. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	LPV/r	↑ prednisolone AUC 31%	Coadministration may be considered if the potential benefits outweigh the risks of adverse effects associated with systemic corticosteroids. If coadministered, monitor for adrenal insufficiency, Cushing's syndrome, and other corticosteroid-associated toxicities.
	All PIs	↑ prednisolone possible	
Betamethasone, Methylprednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	All PIs	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c, ATV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	ATV (unboosted), DRV/c, DRV/r, LPV/r	↔ daclatasvir	No dose adjustment necessary.
	TPV/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.
	DRV	DRV C_{min} ↓ 43% to 48%	**Do not coadminister.**
	LPV/r	Paritaprevir AUC ↑ 117%	**Do not coadminister.**
	ATV/c, DRV/c, TPV/r	No data	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
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	
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Simeprevir	All PIs	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%	**Do not coadminister.**
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir	ATV/r	↔ ATV/r ↔ sofosbuvir Velpatasvir AUC ↑ 2.4-fold	No dose adjustment necessary.
	DRV/r	↔ DRV/r Sofosbuvir AUC ↓ 28% ↔ velpatasvir	No dose adjustment necessary.
	ATV (unboosted), ATV/c, DRV/c, LPV/r	↔ sofosbuvir and velpatasvir expected	No dose adjustment necessary.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected	**Do not coadminister.**
Sofosbuvir/ Velpatasvir/ Voxilaprevir	ATV (unboosted), ATV/c, ATV/r	When Given with ATV/r: • Voxilaprevir AUC ↑ 4.3-fold • Velpatasvir AUC ↑ 93% • Sofosbuvir AUC ↑ 40%	**Do not coadminister.**
	LPV/r	↑ voxilaprevir expected	**Do not coadminister.**
	DRV/c , DRV/r	When Given with DRV/r: • Voxilaprevir AUC ↑ 2.4-fold • ↔ DRV/r, velpatasvir, and sofosbuvir	No dose adjustment needed.
	TPV/r	↓ sofosbuvir expected ↓ velpatasvir expected Effect on voxilaprevir is unknown.	**Do not coadminister.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Contraindicated.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 13 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
Hormonal Contraceptives Oral	ATV (unboosted)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol[b] or 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.
	ATV/r	Ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% Norgestimate ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	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.
	ATV/c	Drospirenone AUC ↑ 2.3-fold Ethinyl estradiol AUC ↓ 22%	**Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.** Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/c	Drospirenone AUC ↑ 1.6-fold Ethinyl estradiol AUC ↓ 30%	Clinical monitoring is recommended due to the potential for hyperkalemia. Consider alternative or additional contraceptive method or alternative ARV.
	DRV/r, LPV/r, TPV/r	Ethinyl estradiol AUC ↓ 37% to 55% Norethindrone AUC ↓ 14% to 34% With TPV/r: • ↔ norethindrone AUC	Consider alternative or additional contraceptive method or alternative ARV drug.
Depot MPA Injectable	LPV/r	MPA AUC ↑ 46% No significant change in C_{min}	No dose adjustment necessary.
Etonogestrel-Releasing Subdermal Implant	LPV/r	Etonogestrel AUC ↑ 52% and C_{min} ↑ 34%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.
Etonogestrel/ Ethinyl Estradiol Vaginal Ring	ATV/r	Ethinyl estradiol AUC ↓ 26% Etonogestrel AUC ↑ 79%	Use standard dose.
Transdermal Ethinyl Estradiol/ Norelgestromin	LPV/r	↔ LPV Ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%	Use standard dose.
	All other PIs	No data	Consider alternative or additional contraceptive method or alternative ARV drug.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Menopausal Hormone Replacement Therapy (HRT)	All PIs	↓ estrogen possible with estradiol or conjugated estrogen (equine and synthetic)	Adjust estrogen dosage as needed based on clinical effects.
	All PIs	↑ drospirenone possible ↑ medroxyprogesterone ↑ micronized progesterone See Hormonal Contraceptives for other progestin-PI interactions	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.
Gender-Affirming Hormone Therapy	All PIs	↓ estradiol possible	Adjust estradiol dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↔ finasteride, goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment necessary.
	All PIs	↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	All PIs	↓ testosterone possible	Adjust testosterone dosage as needed based on clinical effects and endogenous hormone concentrations.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV (unboosted), ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities.
	ATV/c	Atorvastatin AUC ↑ 9.2-fold, C_{max} ↑ 18.9-fold	**Coadministration is not recommended.**
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	DRV/c	Atorvastatin AUC ↑ 3.9-fold, C_{max} ↑ 4.2-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	LPV/r	Atorvastatin AUC ↑ 5.9-fold, C_{max} ↑ 4.7-fold	Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
	TPV/r	Atorvastatin AUC ↑ 9.4-fold, C_{max} ↑ 8.6-fold	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ↔ ATV DRV/r ↓ pitavastatin AUC 26% ↔ DRV/r LPV/r ↓ pitavastatin AUC 20% ↔ LPV	No dose adjustment necessary.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Pravastatin	ATV/c, ATV/r	No data	Titrate pravastatin dose carefully while monitoring for toxicities.
	DRV/c, DRV/r	With DRV/r: • Pravastatin AUC ↑ 81% following single dose of pravastatin • Pravastatin AUC ↑ 23% at steady state	Titrate pravastatin dose carefully while monitoring for toxicities.
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary.
Rosuvastatin	ATV/r	Rosuvastatin AUC ↑ 3-fold, C_{max} ↑ 7-fold	Titrate rosuvastatin dose carefully and use lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 10 mg daily.
	ATV/c	Rosuvastatin AUC ↑ 3.4-fold, C_{max} ↑ 10.6-fold	
	DRV/c	Rosuvastatin AUC ↑ 1.9-fold, C_{max} ↑ 3.8-fold	Titrate rosuvastatin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed rosuvastatin 20 mg daily.
	DRV/r	Rosuvastatin AUC ↑ 48%, C_{max} ↑ 2.4-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	LPV/r	Rosuvastatin AUC ↑ 2.1-fold, C_{max} ↑ 4.7-fold	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed rosuvastatin 10 mg daily.
	TPV/r	Rosuvastatin AUC ↑ 26%, C_{max} ↑ 2.2-fold	No dose adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin expected	**Contraindicated.**
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 16 of 19)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	ATV (unboosted)	Buprenorphine AUC ↑ 93% Norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not coadminister.**
	ATV/r	Buprenorphine AUC ↑ 66% Norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments.
	DRV/r	No significant effect on buprenorphine Norbuprenorphine[d] AUC ↑ 46% and C_{min} ↑ 71%	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.
	LPV/r	No significant effect	
	TPV/r	No significant effect on buprenorphine Norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV level. When transferring buprenorphine from transmucosal delivery to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	PI/c	Effects unknown	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.
Fentanyl	All PIs	↑ fentanyl possible	Clinical monitoring is recommended, including for potentially fatal respiratory depression.
Methadone	ATV (unboosted)	No significant effect	No dose adjustment necessary.
	PI/c	Effects unknown	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.
	All PI/r	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%	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.
Oxycodone	All PIs	Oxycodone AUC ↑ 2.6-fold with LPV/r	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Tramadol	All PIs	↑ tramadol possible	Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 17 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	All PIs except unboosted ATV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold and ↑ C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV (unboosted)	No data	Avanafil dose should not exceed 50 mg once every 24 hours.
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.
Suvorexant	All PIs	↑ suvorexant expected	**Coadministration is not recommended.**

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 18 of 19)

Concomitant Drug	PI	Effect on PI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sedative/Hypnotics, continued			
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	↑ flibanserin 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.

Table 21a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 19 of 19)

[a] DHA is an active metabolite of artemether.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (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.

[c] 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.

[d] Norbuprenorphine is an active metabolite of buprenorphine.

[e] R-methadone is the active form of methadone.

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_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; 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

Table 21b. 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 21c, 22a, and 22b. Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or if a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly.

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.

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	RPV	↓ RPV	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.
PPIs	RPV	With Omeprazole 20 mg Daily: • RPV AUC ↓ 40% and C_{min} ↓ 33%	**Contraindicated. Do not coadminister.**
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin, Doxazosin, Silodosin	EFV, ETR, NVP	↓ alpha antagonist expected	Consider alternative therapy. If coadministration is necessary, monitor for therapeutic effectiveness of alpha antagonist.
Tamsulosin	EFV, ETR, NVP	↓ tamsulosin expected	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.
Anticoagulants/Antiplatelets			
Apixaban	EFV, ETR, NVP	↓ apixaban possible	Consider alternative therapy.
Betrixaban	All NNRTIs	↔ betrixaban expected	No dose adjustment necessary.
Clopidogrel	EFV, ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
	DOR, NVP, RPV	↔ clopidogrel expected	No dose adjustment necessary.
Dabigatran	All NNRTIs	↔ dabigatran expected	No dose adjustment necessary.
Edoxaban	All NNRTIs	↔ edoxaban expected	No dose adjustment necessary.
Prasugrel	All NNRTIs	↔ prasugrel expected	No dose adjustment necessary.
Rivaroxaban	EFV, ETR, NVP	↓ rivaroxaban possible	Consider alternative therapy.
Ticagrelor	EFV, ETR, NVP	↓ ticagrelor expected	Consider alternative therapy.
Warfarin	EFV, ETR, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	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	No dose adjustment necessary.
	DOR, NVP, RPV	↔ expected with DOR, NVP or RPV	No dose adjustment necessary.
Nefazodone	EFV, ETR, NVP	↓ nefazodone expected ↑ NNRTI possible	Monitor the antidepressant effect and titrate dose as necessary. Monitor for ARV-related adverse events.
	DOR, RPV	↑ NNRTI possible	Monitor for ARV-related adverse events.
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.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	↔ fluconazole or EFV	No dose adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dose adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	DOR,RPV	↑ NNRTI possible	No dose adjustment necessary.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole concentration and antifungal response.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
Itraconazole	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35% to 44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	Itraconazole AUC ↓ 61% ↑ NVP possible	Avoid this combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	DOR, ETR, NVP, RPV	↑ NNRTI possible	Monitor for NNRTI toxicities.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** <u>Dose Adjustment</u>: • Voriconazole 400 mg BID, EFV 300 mg daily
	ETR	↔ Voriconazole AUC ETR AUC ↑ 36%	No dose adjustment necessary.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole concentration.
	DOR, RPV	↑ NNRTI possible	No dose adjustment necessary.
Antihyperglycemics			
Canagliflozin, Dapagliflozin, Empagliflozin, Sitagliptin	All NNRTIs	↔ antihyperglycemic expected	No dose adjustment necessary.
Linagliptin, Saxagliptin	EFV, ETR, NVP	↓ antihyperglycemic possible	Monitor glycemic control.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimalarials			
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	**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 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifabutin, continued	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dose adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg Once Daily Compared to RPV 25 mg Once Daily Alone: • ↔ RPV AUC and C_{min}	Increase RPV dose to 50 mg once daily. No dose adjustment for rifabutin.
Rifampin	DOR	DOR AUC ↓ 88%	**Contraindicated.**
	EFV	EFV AUC ↓ 26%	**Do not use EFV 400 mg with rifampin.** Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20% to 58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated.**
Rifapentine	EFV	↔ EFV concentrations	No dose adjustment necessary.
	ETR, NVP	↓ NNRTI possible	**Do not coadminister.**
	DOR, RPV	↓ NNRTI expected	**Contradindicated.**
Antipneumocystis and Antitoxoplasmosis Drugs			
Atovaquone	EFV	Atovaquone AUC ↓ 44% to 47%	Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug. If used in combination, monitor therapeutic efficacy of atovaquone.
Antipsychotics			
Aripiprazole	EFV, ETR, NVP	↓ aripiprazole expected	Monitor effectiveness of antipsychotic. Consider doubling usual dose of aripiprazole over 1–2 weeks. Refer to aripiprazole prescribing information for dosing recommendations.
Brexpiprazole	EFV, ETR, NVP	↓ brexpiprazole expected	Monitor effectiveness of antipsychotic. Consider doubling the usual dose of brexpiprazole and making further adjustments based on clinical response. Refer to brexpiprazole prescribing information.
Cariprazine	EFV, ETR, NVP	↓ cariprazine and ↑ or ↓ active metabolite possible	Coadministration is not recommended.
Olanzapine	EFV	↓ olanzapine possible	Monitor effect of olanzapine.
	DOR, ETR, NVP, RPV	↔ olanzapine expected	No dose adjustment necessary.
Pimozide	EFV, ETR, NVP	↓ pimozide possible	Monitor therapeutic effectiveness of pimozide
Lurasidone, Pimavanserin, Quetiapine, Thioridazine	EFV, ETR, NVP	↓ antipsychotic possible	Monitor effect of antipsychotic.

Table 21b. 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)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	↓ alprazolam possible	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	EFV, NVP	↓ diazepam possible	Monitor for therapeutic effectiveness of diazepam.
	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary. Monitor for diazepam toxicity.
Lorazepam	EFV	↔ lorazepam AUC	No dose adjustment necessary.
	ETR, NVP	↔ lorazepam expected	
Midazolam	EFV	↑ or ↓ midazolam possible	Monitor therapeutic effectiveness and toxicity of midazolam.
	ETR	Midazolam AUC ↓ 31% Midazolam active metabolite C_{max} ↑ 57%	Monitor therapeutic effectiveness of midazolam.
	NVP	↓ midazolam possible	Monitor therapeutic effectiveness of midazolam.
Triazolam	EFV, ETR, NVP	↓ triazolam possible	Monitor therapeutic effectiveness of triazolam.
Cardiac Medications			
Dihydropyridine CCBs	EFV, ETR, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem, Verapamil	EFV	Diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	ETR, NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	DOR, EFV, ETR, NVP	↓ NNRTI possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	EFV, ETR, NVP	Daclatasvir 120 mg Once Daily plus EFV 600 mg Daily Compared with Daclatasvir 60 mg Alone: • Daclatasvir C_{min} ↓ 17%, AUC ↑ 37%	The recommended dose is daclatasvir 90 mg once daily.
	DOR, RPV	No data	No dose adjustment necessary.
Dasabuvir plus Paritaprevir/ Ombitasivir/RTV	DOR	↑ DOR possible	No dose adjustment necessary.
	EFV	No data	**Contraindicated.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150% to 225%	**Do not coadminister,** due to potential for QT interval prolongation with higher concentrations of RPV.

Table 21b. 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)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
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.
Glecaprevir/ Pibrentasvir	DOR	↑ DOR expected	No dose adjustment necessary.
	EFV	↓ glecaprevir and pibrentasvir expected	**Do not coadminister.**
	ETR , NVP	↓ glecaprevir and pibrentasvir possible	
	RPV	↔ glecaprevir, pibrentasvir RPV AUC ↑ 84%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EFV	Ledipasvir AUC, C_{min}, and C_{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_{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_{max} ↓ 37% and C_{min} ↓ 47%	**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_{max} ↓ 37%, and C_{min} ↓ 47% ↓ voxilaprevir expected	**Do not coadminister.**
	ETR, NVP	↓ voxilaprevir expected ↓ velpatasvir expected	**Do not coadminister.**
	DOR, RPV	No signficant effect expected	No dose adjustment necessary.

Table 21b. 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)

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

Table 21b. 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)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Menopausal Hormone Replacement Therapy	EFV, ETR, NVP	↓ 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	Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief.
Gender-Affirming Hormone Therapy	EFV, ETR, NVP	↓ estradiol possible ↔ goserelin, leuprolide acetate, and spironolactone expected ↓ dutasteride and finasteride possible	Monitor feminizing effects of estrogen and antiandrogen therapy and titrate dosing as necessary to achieve therapeutic goals.
	EFV, ETR, NVP	↓ testosterone possible	Monitor masculinizing effects of testosterone and titrate testosterone dose as necessary to achieve therapeutic goals.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	NVP	↓ atorvastatin possible	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	DOR, RPV	↔ atorvastatin AUC	No dose adjustment necessary.
Fluvastatin	EFV, ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin, Simvastatin	EFV	Simvastatin AUC ↓ 68% Simvastatin active metabolite AUC ↓ 60%	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.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	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.
Pitavastatin	EFV	↔ pitavastatin AUC	No dose adjustment necessary.
	DOR, ETR, NVP, RPV	↔ pitavastatin expected	No dose adjustment necessary.
Pravastatin	EFV	Pravastatin AUC ↓ 44%	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.
	ETR	↓ pravastatin possible	
Rosuvastatin	EFV, ETR, NVP	↔ rosuvastatin expected	No dose adjustment necessary.

Table 21b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 10)

Concomitant Drug Class/ Name	NNRTI[a]	Effect on NNRTI and/ or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	EFV, ETR, NVP	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics/Treatments for Opioid Dependence			
Buprenorphine Sublingual or buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine[b] AUC ↓ 71%	No dose adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dose adjustment necessary.
	NVP	No significant effect	No dose adjustment necessary.
Buprenorphine Implant	EFV, ETR, NVP	No data	Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant.
Methadone	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	DOR, ETR	No significant effect	No dose adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% No significant effect on NVP	Opioid withdrawal is common; increased methadone dose is often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dose adjustment necessary, but monitor for withdrawal symptoms.
PDE5 Inhibitors			
Sildenafil	DOR, RPV	↔ sildenafil expected	No dose adjustment necessary.
	ETR	Sildenafil AUC ↓ 57%	May need to titrate sildenafil dose based on clinical effect.
	EFV, NVP	↓ sildenafil possible	
Tadalafil	EFV, ETR, NVP	↓ tadalafil possible	May need to titrate tadalafil dose based on clinical effect.
	RPV	↔ tadalafil	No dose adjustment necessary.
Avanafil, Vardenafil	EFV, ETR, NVP	↓ PDE5 inhibitor possible	May need to increase PDE5 inhibitor dose based on clinical effect.
Miscellaneous Drugs			
Enzalutamide	All NNRTIs	↓ NNRTI expected	**Contraindicated.**
Mitotane	All NNRTIs	↓ NNRTI expected	**Contraindicated.**

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 mg to 150 mg per dose.

[b] Norbuprenorphine is an active metabolite of buprenorphine.

[c] 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_{max} = maximum plasma concentration; C_{min} = 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; PI/r = protease inhibitor/ritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

Table 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018)
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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.

Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Cytomegalovirus and Hepatitis B Antivirals			
Adefovir	TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may increase.
Ganciclovir, Valganciclovir	TAF, TDF	No data	Serum concentrations of ganciclovir and/or TFV may increase. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities.
Hepatitis C Antiviral Agents			
Glecaprevir/Pibrentasvir	TAF, TDF	No significant effect	No dose adjustment necessary.
Ledipasvir/Sofosbuvir, Sofosbuvir/Velpatasvir, Sofosbuvir/Velpatasvir/ Voxilaprevir	TAF	No significant effect	No dose adjustment.
	TDF	Ledipasvir ↑ TFV AUC 40% to 98% when TDF is given with RPV and EFV Further ↑ TFV possible if TDF is given with PIs	No dose adjustment necessary. 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. Consider using TAF in patients at risk of TDF-associated adverse events. If TDF is used in these patients, monitor for TDF toxicity. **Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC is not recommended.**
Ribavirin	TDF	With Sofosbuvir 400 mg: • ↔ TFV AUC	No dose adjustment necessary.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities.
INSTIs			
DTG	TAF	↔ TAF AUC	No dose adjustment necessary.
	TDF	↔ TDF AUC ↔ DTG AUC	No dose adjustment necessary.
RAL	TDF	RAL AUC ↑ 49%	No dose adjustment necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, TDF, TAF, ZDV	No significant effect	No dose adjustment necessary.

Table 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018)
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Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence, continued			
Methadone	ABC	Methadone clearance ↑ 22%	No dose adjustment necessary.
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
Other			
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Anticonvulsants Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	TAF	With Carbamazepine: • TAF AUC ↓ 55% ↓ TAF possible with other anticonvulsants	**Coadministration is not recommended.**
Antimycobacterial Rrifampin	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.**
	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%	No dose adjustment (use TAF 25 mg).
	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 21c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018)
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Concomitant Drug Class/ Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
PIs (HIV), continued			
DRV/c	TAF	TAF 25 mg with DRV/c: • ↔ TAF	No dose adjustment necessary.
	TDF	↑ TDF possible	Monitor for TDF-associated toxicity.
DRV/r	TAF	TAF 10 mg with DRV/r: • ↔ TAF	No dose adjustment necessary.
	TDF	TFV AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF-associated toxicity.
LPV/r	TAF	TAF 10 mg with DRV/r: • TAF AUC ↑ 47%	No dose adjustment necessary.
	TDF	↔ LPV/r AUC TFV AUC ↑ 32%	Clinical significance unknown. Monitor for TDF-associated toxicity.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	TAF	↓ TAF expected	**Coadministration is not recommended.**
	TDF	↔ TDF AUC TPV AUC ↓ 9% to 18% and C_{min} ↓ 12% to 21%	No dose adjustment necessary.
	ZDV	ZDV AUC ↓ 31% to 42% ↔ TPV AUC	Appropriate doses for this combination have not been established.

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; C_{min} = 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 21d. 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.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Tamsulosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tamsulosin expected	**Coadministration is not recommended.** If coadministered, monitor for tamsulosin toxicities.
Terazosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose and titrate while monitoring for clinical response/toxicity. Dose reduction may be necessary.
Silodosin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ silodosin expected	**Contraindicated.**
Acid Reducers			
Al, Mg, +/- Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	BIC	↔ BIC AUC if antacid is given 2 hours after BIC and under fasting conditions BIC AUC ↓ 79% if given simultaneously with antacid BIC AUC ↓ 52% if antacid is given 2 hours before BIC	With Antacids Containing Al/Mg or Ca: • BIC can be taken under fasting conditions at least 2 hours before antacids containing Al/Mg or Ca. Do not coadminister BIC simultaneously with, or 2 hours after, antacids containing Al/Mg or Ca.
	DTG	DTG AUC ↓ 74% if given simultaneously with antacid DTG AUC ↓ 26% if given 2 hours before antacid	Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if given simultaneously with antacid EVG AUC ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c/TDF/FTC and antacid administration by >2 hours.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Al, Mg, +/- Ca-Containing Antacids, continued Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe, Ca supplements, multivitamins).	RAL	Al/Mg Hydroxide Antacid: • RAL C_{min} ↓ 49% to 63% $CaCO_3$ Antacid: • RAL (400 mg BID) C_{min} ↓ 32% • RAL (1200 mg once daily) C_{min} ↓ 48% to 57%	**Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent. With $CaCO_3$ Antacids: • RAL 1200 mg once daily: **Do not coadminister.** • RAL 400 mg BID: No dose adjustment or separation necessary.
H2-Receptor Antagonists	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment necessary.
PPIs	BIC, DTG, EVG/c	No significant effect	No dose adjustment necessary.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment necessary.
Anticoagulants and Antiplatelets			
Apixaban	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ apixaban 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	No dose adjustment necessary.
	EVG/c	↑ betrixaban expected	Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily.
Dabigatran	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dabigatran expected Dabigatran AUC ↑ 110% to 127% with COBI 150 mg alone	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	No dose adjustment necessary.
	EVG/c	↔ or ↑ edoxaban 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.
	EVG/c	↑ rivaroxaban expected	**Coadministration is not recommended.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Ticagrelor	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ticagrelor expected	**Coadministration is not recommended.**
Vorapaxar	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ vorapaxar expected	**Coadministration is not recommended.**
Warfarin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	Consider using an alternative anticonvulsant or ARV.
	DTG	DTG AUC ↓ 49%	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.
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Ethosuximide	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ethosuximide possible	Clinically monitor for ethosuximide toxicities.
Lamotrigine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	Monitor anticonvulsant level and adjust dose accordingly.
Oxcarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider using an alternative anticonvulsant or ARV.
Phenobarbital **Phenytoin**	BIC	↓ BIC possible	**Coadministration is not recommended.**
	DTG	↓ DTG possible	**Coadministration is not recommended.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Coadministration is not recommended.**
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 4 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Aripiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. 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.
Brexpiprazole	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. 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.
Bupropion	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Cariprazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cariprazine expected	<u>Starting Cariprazine in a Patient Already on EVG/c</u>: • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. • From Day 4 onward, administer 1.5 mg daily. Can be increased to a maximum dose of 3 mg daily. • If EVG/c is withdrawn, cariprazine dose may need to be increased. <u>Starting EVG/c in a Patient Already on Cariprazine</u>: • For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half. • For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily. • For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day. • If EVG/c is withdrawn, cariprazine dose may need to be increased.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 5 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants/Anxiolytics/Antipsychotics, continued Also see Sedative/Hypnotics section below.			
Fluvoxamine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Lurasidone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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.
	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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	No dose adjustment necessary.
		↑ other SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	BIC, DTG, RAL	↔ BIC, DTG, RAL expected ↔ SSRI expected	No dose adjustment necessary.
TCAs Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ 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 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 6 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Isavuconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
Posaconazole	BIC	↑ BIC expected	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister voriconazole and COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for metformin adverse effects.
	DTG	DTG 50 mg Once Daily plus Metformin 500 mg BID: • Metformin AUC ↑ 79% and C_{max} ↑ 66% DTG 50 mg BID plus Metformin 500 mg BID: • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for metformin adverse effects. 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.
	RAL	↔ expected	No dose adjustment necessary.
Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/ Saxagliptin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ saxagliptin expected	**Do not coadminister**, as this coformulated drug contains 5 mg of saxagliptin.
Antimycobacterials			
Clarithromycin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ clarithromycin possible ↑ COBI possible	CrCl 50–60 mL/min: • Reduce clarithromycin dose by 50% CrCl <50 mL/min: • EVG/c **is not recommended.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 7 of 15)

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

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 8 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications			
Antiarrhythmics Amiodarone, bepridil, digoxin, disopyramide, dronedarone, flecainide, systemic lidocaine, mexilitine, propafenone, quinidine	BIC, DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment necessary. Coadminister with caution. Clinical monitoring is recommended.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment necessary.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and no significant change in AUC	Use antiarrhythmics with caution. TDM, if available, is recommended for antiarrhythmics.
Bosentan	BIC, DTG	↓ BIC, DTG possible	Standard doses.
	RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ bosentan possible	<u>In Patients on EVG/c ≥10 Days</u>: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. <u>In Patients on Bosentan Who Require EVG/c</u>: • 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.
Beta-blockers (e.g., metoprolol, timolol)	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ beta-blockers possible	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).
CCBs	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment necessary.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 21a for diltiazem plus ATV/r recommendations.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ranolazine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ranolazine expected	**Contraindicated.**
Ivabradine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ ivabradine expected	**Contraindicated.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 9 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, DTG, EVG/c, RAL	↔ expected	No dose adjustment necessary.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoid possible	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).
Betamethasone, Budesonide Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids possible ↓ EVG possible	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.**
Dexamethasone Systemic	BIC	↓ BIC possible	Consider an alternative corticosteroid for long-term use or an alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↓ EVG and COBI possible	Consider an alternative corticosteroid for long-term use or alternative ART. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ prednisolone possible	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.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ daclatasvir	No dose adjustment necessary.
	EVG/c	↑ daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	BIC, RAL	No data	No dose adjustment necessary.
Dasabuvir plus Ombitasvir/ Paritaprevir/RTV	BIC, DTG	No data	No dose adjustment necessary.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 10 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment necessary.
	EVG/c	↑ elbasvir and ↑ grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ elbasvir ↔ grazoprevir ↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment necessary.
Glecaprevir/ Pibrentasvir	BIC	↔ BIC expected	No dose adjustment necessary.
	DTG, RAL	No significant effect	No dose adjustment necessary.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment necessary.
Ledipasvir/ Sofosbuvir	EVG/c/TDF/ FTC	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/TAF/ FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment necessary.
	BIC, DTG, RAL	↔ DTG or RAL	No dose adjustment necessary.
Simeprevir	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
Sofosbuvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir	All INSTIs	↔ expected	No dose adjustment necessary.
Sofosbuvir/ Velpatasvir/ Voxilaprevir	EVG/c	When Given with Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg: • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment necessary.
	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI possible	**Contraindicated.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 11 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies			
Hormonal Contraceptives Oral	BIC, DTG, RAL	↔ ethinyl estradiol, norgestimate, and DTG or RAL	No dose adjustment necessary.
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and 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.
Hormonal Contraceptives Non-oral	All INSTIs	No data	No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear if oral drug-drug interaction data can be extrapolated beyond oral routes of administration.
Menopausal Hormone Replacement Therapy	BIC, DTG, RAL	With Estradiol or Conjugated Estrogen (Equine and Synthetic): • ↔ estrogen expected ↔ drospirenone, medroxyprogesterone, or micronized progesterone expected	No dose adjustment necessary.
	EVG/c	↓ estrogen expected ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Gender-Affirming Hormone Therapy	BIC, DTG, RAL	↔ estrogen expected	No dose adjustment necessary.
	BIC, DTG, EVG/c, RAL	↔ finasteride, goserelin, leuprolide acetate, spironolactone expected	
	EVG/c	↓ estradiol expected ↑ dutasteride possible	Adjust dutasteride dosage as needed based on clinical effects and endogenous hormone concentrations.
	EVG/c	↑ testosterone possible	Monitor masculinizing effects of testosterone and for adverse effects and adjust testosterone dose as necessary.
	BIC, DTG, RAL	↔ testosterone expected	No dose adjustment necessary.
HMG-CoA Reductase Inhibitors			
Atorvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities. Do not exceed 20 mg atorvastatin daily.
Lovastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated**.
Pitavastatin, Pravastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	No dose recommendation.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 12 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest dose necessary while monitoring for toxicities.
Simvastatin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated**.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ immunosuppressant possible	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.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, DTG	↔ expected	No dose adjustment necessary.
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42% and C_{min} ↑ 57%	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.
	RAL	↔ observed (sublingual) ↔ expected (implant)	No dose adjustment necessary.
Methadone	All INSTIs	No significant effect	No dose adjustment necessary.
PDE5 Inhibitors			
Avanafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	No data	**Coadministration is not recommended.**
Sildenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ sildenafil expected	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.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 13 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ tadalafil expected	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 EVG/c >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/c:* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ benzodiazepines possible	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.
Midazolam, Triazolam	BIC, RAL	↔ expected	No dose adjustment necessary.
	DTG	With DTG 25 mg: • ↔ Midazolam AUC	No dose adjustment necessary.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**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 >1 dose is administered.
Suvorexant	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 14 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Calcifediol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required, and serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations should be closely monitored.
Cisapride	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ cisapride expected	**Contraindicated.**
Colchicine	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For Treatment of Gout Flares: • 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. For Prophylaxis of Gout Flares: • 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. For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.
Enzalutamide	DTG	↓ DTG possible	Monitor for ARV efficacy.
	BIC, EVG/c	↓ BIC, EVG/c expected	**Contraindicated.**
	RAL	↔ expected	No dose adjustment necessary.
Ergot Derivatives	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dihydroergotamine, ergotamine, methylergonovine expected	**Contraindicated.**
Dronabinol	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse effects.
Eluxadoline	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse effects.
Flibanserin	BIC, DTG, RAL	↔ expected	No dose adjustment necessary.
	EVG/c	↑ flibanserin expected	**Contraindicated.**
Mitotane	BIC, EVG/c	↓ BIC and ↓ EVG/c expected	**Contraindicated.**
	DTG	↓ DTG possible	Monitor for ARV efficacy.
	RAL	↔ expected	No dose adjustment necessary.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated October 25, 2018; last reviewed October 25, 2018) (page 15 of 15)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
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 $CaCO_3$ 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.
	EVG/c	↑ salmeterol possible	**Do not coadminister**, due to potential increased risk of salmeterol-associated cardiovascular events.

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; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; 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 21e. 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.

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine, Phenobarbital, Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungals			
Isavuconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Itraconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Posaconazole	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID.
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, no dose adjustment is necessary. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Dose: • MVC 600 mg BID If used with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	**Do not coadminister.**
Hepatitis C Direct-Acting Antivirals			
Daclatasvir	MVC	↔ MVC expected ↔ daclatasvir expected	No dose adjustment necessary.
Dasabuvir plus Ombitasvir/Paritaprevir/ RTV	MVC	↑ MVC expected	**Do not coadminister.**
Elbasvir/Grazoprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Ledipasvir/Sofosbuvir	MVC	↔ MVC expected	No dose adjustment necessary.
Glecaprevir/Pibrentasvir	MVC	↔ MVC expected	No dose adjustment necessary.
Simeprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Sofosbuvir	MVC	↔ MVC expected	No dose adjustment necessary.
Sofosbuvir/Velpatasvir	MVC	↔ MVC expected	No dose adjustment necessary.

Table 21e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 3)

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antivirals, continued			
Sofosbuvir/Velpatasvir/ Voxilaprevir	MVC	↔ MVC expected	No dose adjustment necessary.
Herbal Products			
St. John's Wort	MVC	↓ MVC expected	**Do not coadminister.**
Hormonal Therapies			
Hormonal Contraceptives	MVC	↔ Ethinyl estradiol or levonorgestrel	No dose adjustment necessary.
Menopausal Hormone Replacement Therapy	MVC	↔ MVC or hormone replacement therapies expected	No dose adjustment necessary.
Gender-Affirming Hormone Therapies	MVC	↔ MVC or gender-affirming hormones expected	No dose adjustment necessary.
ARV Drugs			
INSTIs			
BIC, DTG	MVC	↔ MVC expected	No dose adjustment necessary.
EVG/c	MVC	↑ MVC possible	Dose: • MVC 150 mg BID
RAL	MVC	MVC AUC ↓ 21% RAL AUC ↓ 37%	No dose adjustment necessary.
NNRTIs			
DOR, RPV	MVC	↔ MVC expected	No dose adjustment necessary.
EFV	MVC	MVC AUC ↓ 45%	Dose: • MVC 600 mg BID
ETR	MVC	MVC AUC ↓ 53%	Dose: • MVC 600 mg BID in the absence of a potent CYP3A inhibitor
NVP	MVC	↔ MVC AUC	Without HIV PI: • MVC 300 mg BID With HIV PI (Except TPV/r): • MVC 150 mg BID
PIs			
ATV with or without RTV or COBI	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV/r 300 mg/100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: • MVC 150 mg BID

Table 21e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated October 25, 2018; last reviewed October 25, 2018) (page 3 of 3)

Concomitant Drug Class/ Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PIs, continued			
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 22a. 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.

PIs		NNRTIs				
		DOR	**EFV**	**ETR**	**NVP**	**RPV[a]**
ATV Unboosted	**PK Data**	↑ DOR expected ↔ ATV expected	↔ EFV ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ATV AUC ↓ 17% and C_{min} ↓ 47%	↓ ATV possible	↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/c	**PK Data**	↑ DOR expected ↔ ATV expected	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↓ ATV possible ↓ COBI possible	↑ RPV possible ↔ ATV expected
	Dose	Standard doses	EFV standard dose In ART-Naive Patients: • ATV 400 mg plus COBI 150 mg once daily • **Do not use coformulated ATV/c 300 mg/150 mg.** In ART-Experienced Patients: • **Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/r	**PK Data**	↑ DOR expected ↔ ATV expected	(ATV 400 mg plus RTV 100 mg) Once Daily: • ATV concentrations similar to (ATV 300 mg plus RTV 100 mg) without EFV	(ATV 300 mg plus RTV 100 mg) Once Daily: • ETR AUC and C_{min} both ↑ ~30% • ↔ ATV AUC and C_{min}	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible
	Dose	Standard doses	EFV standard dose In ART-Naive Patients: • (ATV 400 mg plus RTV 100 mg) once daily In ART-Experienced Patients: • **Do not coadminister.**	ETR standard dose (ATV 300 mg plus RTV 100 mg) once daily	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	↑ DOR expected ↔ DRV expected	↓ DRV possible ↓ COBI possible	ETR 400 mg Once Daily with (DRV 800 mg plus COBI 150 mg) Once Daily: • ↔ ETR AUC and C_{min} • ↔ DRV AUC and C_{min} ↓ 56% • COBI AUC ↓ 30% and C_{min} ↓ 66%	↓ DRV possible ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses

Table 22a. Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

PIs		NNRTIs				
		DOR	EFV	ETR	NVP	RPV[a]
DRV/r	**PK Data**	↑ DOR expected ↔ DRV expected	With (DRV 300 mg plus RTV 100 mg) BID: • EFV AUC ↑ 21% • ↔ DRV AUC and C_{min} ↓ 31%	ETR 100 mg BID with (DRV 600 mg plus RTV 100 mg) BID: • ETR AUC ↓ 37% and C_{min} ↓ 49% • ↔ DRV	With (DRV 400 mg plus RTV 100 mg) BID: • NVP AUC ↑ 27% and C_{min} ↑ 47% • DRV AUC ↑ 24%[b]	RPV 150 mg Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily: • RPV AUC ↑ 130% and C_{min} ↑ 178% • ↔ DRV
	Dose	Standard doses	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard doses Despite reduced ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	Standard doses	Standard doses
LPV/r	**PK Data**	↑ DOR expected ↔ LPV expected	With LPV/r Tablets 500 mg/125 mg[c] BID: • LPV concentration similar to that of LPV/r 400 mg/100 mg BID without EFV	With LPV/r Tablets: • ETR AUC ↓ 35% (comparable to the decrease with DRV/r) • ↔ LPV AUC	With LPV/r Capsules: • LPV AUC ↓ 27% and C_{min} ↓ 51%	RPV 150 mg Once Daily with LPV/r Capsules: • RPV AUC ↑ 52% and C_{min} ↑ 74% • ↔ LPV
	Dose	Standard doses	LPV/r tablets 500 mg/125 mg[c] BID; LPV/r oral solution 533 mg/133 mg BID EFV standard dose	Standard doses	LPV/r tablets 500 mg/125 mg[c] BID; LPV/r oral solution 533 mg/133 mg BID NVP standard dose	Standard doses
TPV/r Always use TPV with RTV	**PK Data**	↑ DOR expected ↔ TPV expected	With (TPV 500 mg plus RTV 100 mg) BID: • ↔ EFV • TPV AUC ↓ 31% and C_{min} ↓ 42% With (TPV 750 mg plus RTV 200 mg) BID: • ↔ EFV and TPV	With (TPV 500 mg plus RTV 200 mg) BID: • ETR AUC ↓ 76% and C_{min} ↓ 82% • ↔ TPV AUC and C_{min} ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID *or* with (TPV 750 mg plus RTV 100 mg) BID: • ↔ NVP • ↔ TPV expected	↑ RPV possible
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses	Standard doses

[a] Approved dose for RPV is 25 mg once daily. Most PK studies were performed using RPV 75 mg to 150 mg per dose.

[b] DRV concentration was compared to a historic control.

[c] 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_{min} = 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

Table 22b. 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.

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs					
DOR	**PK Data**	↔ DOR, BIC expected	↔ DOR DTG AUC ↑ 36% and C_{min} ↑ 27%	↑ DOR expected ↔ EVG	↔ DOR, RAL expected
	Dose	Standard doses	Standard doses	Standard doses	Standard doses
EFV	**PK Data**	↓ BIC expected	With DTG 50 mg Once Daily: • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, EFV possible	With RAL 400 mg BID: • RAL AUC ↓ 36% and C_{min} ↓ 21% With RAL 1200 mg Once Daily: • RAL AUC ↓ 14% and ↔ C_{min}
	Dose	**Do not coadminister.**	In Patients Without INSTI Resistance: • DTG 50 mg BID In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance: **• Consider alternative combination.**	**Do not coadminister.**	Standard doses
ETR	**PK Data**	↓ BIC expected	ETR 200 mg BID plus DTG 50 mg Once Daily: • DTG AUC ↓ 71% and C_{min} ↓ 88% ETR 200 mg BID with (DRV 600 mg plus RTV 100 mg) BID and DTG 50 mg Once Daily: • DTG AUC ↓ 25% and C_{min} ↓ 37% ETR 200 mg BID with (LPV 400 mg plus RTV 100 mg) BID and DTG 50 mg Once Daily: • DTG AUC ↑ 11% and C_{min} ↑ 28%	↑ or ↓ EVG, COBI, ETR possible	ETR 200 mg BID plus RAL 400 mg BID: • ETR C_{min} ↑ 17% • RAL C_{min} ↓ 34%

Table 22b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 3)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
NNRTIs, continued					
ETR, continued	**Dose**	**Do not coadminister.**	**Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.** In Patients Without INSTI Resistance: • DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) In Patients With Certain INSTI-Associated Resistancea or Clinically Suspected INSTI Resistance: • DTG 50 mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**
NVP	**PK Data**	↓ BIC expected	With DTG 50 mg Once Daily: • DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, NVP possible	No data
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
RPV	**PK Data**	No data	With DTG 50 mg Once Daily: • DTG AUC ↔ and C_{min} ↑ 22% • RPV AUC ↔ and C_{min} ↑ 21%	↑ or ↓ EVG, COBI, RPV possible	↔ RPV RAL C_{min} ↑ 27%
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses
PIs					
ATV/c	**PK Data**	BIC AUC ↑ 305%	No data	No data	No data
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
ATV +/- RTV	**PK Data**	BIC AUC ↑ 310%	Unboosted ATV plus DTG 30 mg Once Daily: • DTG AUC ↑ 91% and C_{min} ↑ 180% (ATV 300 mg plus RTV 100 mg) Once Daily plus DTG 30 mg Once Daily: • DTG AUC ↑ 62% and C_{min} ↑ 121%	↑ or ↓ EVG, COBI, ATV possible	With Unboosted ATV: • RAL AUC ↑ 72% With Unboosted ATV and RAL 1200 mg: • RAL AUC ↑ 67% With (ATV 300 mg plus RTV 100 mg) Once Daily: • RAL AUC ↑ 41%
	Dose	**Do not coadminister.**	Standard doses	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	BIC AUC ↑ 74%	DRV/c plus DTG Once Daily: • ↔ DTG, DRV, COBI DTG 50 mg Once Daily and DRV/r Once Daily Switched to DRV/c: • DTG C_{min} ↑ 100%	DRV/c plus EVG/c: • ↓ EVG possible	No data
	Dose	Standard doses	Standard doses	**Do not coadminister.**	Standard doses

Table 22b. 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)

ARV Drugs by Drug Class		INSTIs			
		BIC	DTG	EVG/c	RAL
PIs, continued					
DRV/r	**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
LPV/r	**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
TPV/r	**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 In Patients With Certain INSTI-Associated Resistance[a] or Clinically Suspected INSTI Resistance: **• Consider alternative combination.**	**Do not coadminister.**	RAL 400 mg BID **Coadministration with RAL 1200 mg once daily is not recommended.**

[a] 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 = rilpivirine; RTV = ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

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

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

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

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

Appendix A: Key to Acronyms (Last updated July 10, 2019; last reviewed July 10, 2019)

Drug Name Abbreviations

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

General Terms

Abbreviation	Definition
17-BMP	beclomethasone 17-monopropionate
ADAP	AIDS drug assistance program

Ag/Ab	antigen/antibody
Al	aluminum
ALT	alanine aminotransferase
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AUD	alcohol use disorder
AV	atrioventricular
AWP	average wholesale price
BID	twice daily
BMD	bone mineral density
BUN	blood urea nitrogen
Ca	calcium
$CaCO_3$	calcium carbonate
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAA	direct-acting antiviral
DHA	dihydroartemisinin
DILI	drug-induced liver injury
DMPA	depot medroxyprogesterone acetate

DOT	directly observed therapy
EBV	Epstein-Barr virus
EC	enteric coated
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	fixed-dose combination
Fe	iron
FI	fusion inhibitor
FUL	federal upper limit
GAHT	gender-affirming hormone therapy
GAZT	azidothymidine glucuronide
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
HAD	HIV-associated dementia
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO_3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV RNA	HIV viral load
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVAN	HIV-associated nephropathy
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HRT	hormone replacement therapy
HSR	hypersensitivity reaction
HTLV-1	human T-lymphotropic virus-1
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
K	potassium

KS	Kaposi's sarcoma
LDL	low-density lipoprotein
LLOD	lower limits of detection
MAC	*Mycobacterium avium* complex
MAT	medication-assisted treatment
MATE	multidrug and toxin extrusion transporter
MDMA	methylenedioxymethamphetamine
Mg	magnesium
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRI	magnetic resonance imaging
msec	millisecond
MSM	men who have sex with men
MTR	multi-tablet regimen
Na	sodium
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OAT	opioid agonist therapy
OATP	organic anion-transporting polypeptide
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
OI	opportunistic infection
ONDCP	Office of National Drug Control Policy
OR	odds ratio
OTP	opioid treatment program
OUD	opioid use disorder
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDE5	phosphodiesterase type 5
PI	protease inhibitor
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic
PO	orally
PPI	proton pump inhibitor
PR	protease
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone

q(n)d	every (n) days
q(n)h	every (n) hours
QTc	QT corrected for heart rate
RNA	ribonucleic acid
RR	relative risk
RT	reverse transcriptase
SAMHSA	Substance Abuse and Mental Health Services Administration
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
STR	single-tablet regimen
SUD	substance use disorder
TB	tuberculosis
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
UGT	uridine diphosphate glucuronosyltransferase
VPA	valproic acid
WAC	wholesale acquisition cost
WHO	World Health Organization
XR	extended release
Zn	zinc

Appendix B, Table 1. Coformulated Single-Tablet Regimens (Last updated July 10, 2019; last reviewed July 10, 2019)

The following table includes dose recommendations for FDA-approved STR products. Please see the class-specific drug characteristics tables (Appendix B, Tables 3 to 6) for details about the individual drugs contained in these STR products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. Drugs listed in this table are arranged **in alphabetical order** by trade name within each section.

Trade Name (Abbreviations)	ARV Drugs Included in the STR	Dosing Recommendation[a]
INSTI plus Two NRTIs		
Biktarvy (BIC/TAF/FTC)	Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily
Genvoya (EVG/c/TAF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet once daily with food
Stribild (EVG/c/TDF/FTC)	Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily with food
Triumeq (DTG/ABC/3TC)	Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg	One tablet once daily
INSTI plus One NRTI		
Dovato (DTG/3TC)	Dolutegravir 50 mg/lamivudine 300 mg	One tablet once daily
PI plus Two NRTIs		
Symtuza (DRV/c/TAF/FTC)	Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg	One tablet once daily with food
NNRTI plus Two NRTIs		
Atripla (EFV/TDF/FTC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily on an empty stomach, preferably at bedtime
Complera (RPV/TDF/FTC)	Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily with a meal
Delstrigo (DOR/TDF/3TC)	Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Odefsey (RPV/TAF/FTC)	Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily with a meal
Symfi (EFV/TDF/3TC)	Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily on an empty stomach, preferably at bedtime
Symfi Lo (EFV/TDF/3TC)	Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily on an empty stomach, preferably at bedtime
INSTI plus One NNRTI		
Juluca (DTG/RPV)	Dolutegravir 50 mg/rilpivirine 25 mg	One tablet once daily with a meal

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the STR can be taken with or without food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; c = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Appendix B, Table 2. Nucleoside Reverse Transcriptase Inhibitor-Based, Fixed-Dose Combination Tablets for Use as Part of an Antiretroviral Regimen (Last updated July 10, 2019; last reviewed July 10, 2019)

The following table includes dose recommendations for FDA-approved, dual-NRTI FDC products. These FDC tablets **are not complete regimens** and must be administered in combination with other ARV drugs.

Please see the class-specific drug characteristics tables (Appendix B, Tables 3 to 6) for details about the individual drugs contained in these FDC products, including information on elimination and metabolic pathways, serum and intracellular half-lives, and adverse effects. Drugs listed in this table are arranged **in alphabetical order** by trade names within each section.

Trade Name (Abbreviations)	ARV Drugs Included in the FDC Tablet	Dosing Recommendation[a]
TAF or TDF plus an NRTI		
Descovy (TAF/FTC)	Tenofovir alafenamide 25 mg/emtricitabine 200 mg	One tablet once daily
Cimduo (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Temixys (TDF/3TC)	Tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg	One tablet once daily
Truvada (TDF/FTC)	Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg	One tablet once daily
Other NRTI-Based FDC Tablets		
Epzicom (ABC/3TC) **Note:** Generic is available.	Abacavir 600 mg/lamivudine 300 mg	One tablet once daily
Combivir (ZDV/3TC) **Note:** Generic is available.	Zidovudine 300 mg/lamivudine 150 mg	One tablet twice daily

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. All FDC tablets listed in this table can be taken without regard to food.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 1 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic tablet formulation is available.	**Ziagen:** • 300 mg tablet • 20 mg/mL oral solution **FDC Tablets that Contain ABC:**[c] • Epzicom (ABC/3TC) • Trizivir (ABC/ZDV/3TC) Also available as part of the STR Triumeq (DTG/ABC/3TC)[c]	**Ziagen:** • ABC 600 mg once daily, *or* • ABC 300 mg twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain ABC.	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 10).	1.5 hours/12–26 hours	Patients who test positive for HLA-B*5701 are at the highest risk of experiencing HSRs. HLA screening should be done before initiating ABC. For patients with a history of HSRs, re-challenge **is not recommended**. Symptoms of HSRs may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (e.g., sore throat, cough, or shortness of breath). Some cohort studies suggest an increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic delayed-release capsules are available; the dose for these is the same as for Videx EC.	**Videx EC:** • 125, 200, 250, and 400 mg capsules **Videx:** • 10 mg/mL oral solution	*Body Weight ≥60 kg* Without TDF: • ddI 400 mg once daily With TDF: • ddI 250 mg once daily *Body Weight <60 kg* Without TDF: • ddI 250 mg once daily With TDF: • ddI 200 mg once daily Take ddI a half an hour before or 2 hours after a meal. Oral solution should be administered twice daily, with the total daily dose divided into two doses.	Renal excretion: 50% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	1.5 hours/>20 hours	Pancreatitis Peripheral neuropathy Retinal changes, optic neuritis Lactic acidosis with hepatic steatosis with or without pancreatitis (this is a 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 an 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 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 2 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva*	**Emtriva:** • 200 mg hard gelatin capsule • 10 mg/mL oral solution **FDC Tablets that Contain FTC:[c]** • Descovy (TAF/FTC) • Truvada (TDF/FTC) **STRs that Contain FTC:[d]** • Atripla (EFV/TDF/FTC) • Biktarvy (BIC/TAF/FTC) • Complera (RPV/TDF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Stribild (EVG/c/TDF/FTC) • Symtuza (DRV/c/TAF/FTC)	**Emtriva** *Capsule:* • FTC 200 mg once daily *Oral Solution:* • FTC 240 mg (24 mL) once daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain FTC.	Renal excretion: 86% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	10 hours/>20 hours	Minimal toxicity Hyperpigmentation/skin discoloration Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue FTC.
Lamivudine (3TC) *Epivir* **Note:** Generic is available.	**Epivir:** • 150 and 300 mg tablets • 10 mg/mL oral solution **FDC Tablets that Contain 3TC:[c]** • Cimduo (TDF/3TC) • Combivir (ZDV/3TC) • Epzicom (ABC/3TC) • Temixys (TDF/3TC) • Trizivir (ABC/ZDV/3TC) **STRs that Contain 3TC:[d]** • Delstrigo (DOR/TDF/3TC) • Dovato (DTG/3TC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC) • Triumeq (DTG/ABC/3TC)	**Epivir:** • 3TC 300 mg once daily, *or* • 3TC 150 mg twice daily See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain 3TC.	Renal excretion: 70% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	5–7 hours/ 18–22 hours	Minimal toxicity Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue 3TC.

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 3 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Stavudine (d4T) *Zerit* **Note:** Generic is available.	**Zerit:** • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	*Body Weight ≥60 kg:* • d4T 40 mg twice daily *Body Weight <60 kg:* • d4T 30 mg twice daily WHO recommends 30-mg, twice-daily dose regardless of body weight.	Renal excretion: 50% Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	1 hour/7.5 hours	Peripheral neuropathy Lipoatrophy Pancreatitis Lactic acidosis/severe hepatomegaly with hepatic steatosis (this is a rare, but potentially life-threatening, toxicity) Hyperlipidemia Insulin resistance/diabetes mellitus Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Alafenamide (TAF) *Vemlidy* **Note:** Vemlidy is available as a 25-mg tablet for the treatment of HBV.	**STRs that Contain TAF:**[d] • Biktarvy (BIC/TAF/FTC) • Genvoya (EVG/c/TAF/FTC) • Odefsey (RPV/TAF/FTC) • Symtuza (DRV/c/TAF/FTC) Also available as part of the FDC tablet Descovy (TAF/FTC)[c]	See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TAF.	Metabolized by cathepsin A. **Not recommended** in patients with CrCl <30 mL/min.	0.5 hours/150–180 hours	Renal insufficiency, Fanconi syndrome, and proximal renal tubulopathy are less likely to occur with TAF than with TDF. Osteomalacia and decrease in bone mineral density are less likely to occur with TAF than with TDF. Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TAF. Diarrhea, nausea, headache
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Note:** Generic is available.	**Viread:** • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder **Generic:** • 300 mg tablet **FDC Tablets that Contain TDF:**[c] • Cimduo (TDF/3TC) • Temixys (TDF/3TC) • Truvada (TDF/FTC) **STRs that Contain TDF:**[d] • Atripla (EFV/TDF/FTC) • Complera (RPV/TDF/FTC) • Delstrigo (DOR/TDF/3TC) • Stribild (EVG/c/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	Viread: • TDF 300 mg once daily, *or* • 7.5 level scoops of oral powder once daily (dosing scoop dispensed with each bottle; one level scoop contains 1 g of oral powder). Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.** See Appendix B, Tables 1 and 2 for dosing information for FDC tablets that contain TDF.	Renal excretion is the primary route of elimination. Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	17 hours/>60 hours	Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy Osteomalacia, decrease in bone mineral density Severe acute exacerbation of hepatitis may occur in patients with HBV/HIV coinfection who discontinue TDF. Asthenia, headache, diarrhea, nausea, vomiting, flatulence

Appendix B, Table 3. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 4 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic is available.	**Retrovir:** • 100 mg capsule • 10 mg/mL IV solution • 10 mg/mL oral solution **Generic:** • 300 mg tablet **FDC Tablets that Contain ZDV:**[c] • Combivir (ZDV/3TC) • Trizivir (ABC/ZDV/3TC)	**Retrovir:** • ZDV 300 mg twice daily, *or* • ZDV 200 mg three times a day See Appendix B, Table 2 for dosing information for FDC tablets that contain ZDV.	Metabolized to GAZT Renal excretion of GAZT Dose adjustment is recommended in patients with renal insufficiency (see Appendix B, Table 10).	1.1 hours/7 hours	**Bone Marrow Suppression:** Macrocytic anemia or neutropenia Nausea, vomiting, headache, insomnia, asthenia Nail pigmentation Lactic acidosis/severe hepatomegaly with hepatic steatosis (this is a rare, but potentially life-threatening, toxicity) Hyperlipidemia Insulin resistance/diabetes mellitus Lipoatrophy Myopathy

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 2 for information about these formulations.

[d] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; c = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; 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; IV = intravenous; MI = myocardial infarction; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization; ZDV = zidovudine

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 1 of 2)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Doravirine (DOR) *Pifeltro*	**Pifeltro:** • 100 mg tablet Also available as part of the STR Delstrigo (DOR/TDF/3TC)[c]	**Pifeltro:** • One tablet once daily See Appendix B, Table 1 for dosing information for Delstrigo.	CYP3A4/5 substrate	15 hours	Nausea Dizziness Abnormal dreams
Efavirenz (EFV) *Sustiva* **Note:** Generic is available.	**Sustiva:** • 50 and 200 mg capsules • 600 mg tablet **Generic:** • 600 mg tablet **STRs that Contain EFV:**[c] • Atripla (EFV/TDF/FTC) • Symfi (EFV 600 mg/TDF/3TC) • Symfi Lo (EFV 400 mg/TDF/3TC)	**Sustiva:** • EFV 600 mg once daily, at or before bedtime Take on an empty stomach to reduce side effects See Appendix B, Table 1 for dosing information for STRs that contain EFV.	Metabolized by CYP2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2B6 and 2C19 inducer	40–55 hours	Rash[d] Neuropsychiatric symptoms[e] Serum transaminase elevations Hyperlipidemia Use of EFV may lead to false-positive results with some cannabinoid and benzodiazepine screening assays QT interval prolongation
Etravirine (ETR) *Intelence*	**Intelence:** • 25, 100, and 200 mg tablets	**Intelence:** • ETR 200 mg twice daily Take following a meal.	CYP3A4, 2C9, and 2C19 substrate CYP3A4 inducer CYP2C9 and 2C19 inhibitor	41 hours	Rash, including Stevens-Johnson syndrome[d] HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure), have been reported. Nausea

Appendix B, Table 4. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 2 of 2)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Nevirapine (NVP) *Viramune* or *Viramune XR* **Note:** Generic 200-mg tablets and oral suspension are available.	**Viramune:** • 200 mg tablet • 50 mg/5 mL oral suspension **Viramune XR:** • 400 mg tablet	**Viramune:** • NVP 200 mg once daily for 14 days (lead-in period); thereafter, NVP 200 mg twice daily, *or* • NVP 400 mg (Viramune XR tablet) once daily Take without regard to meals. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves, but do not administer for longer than 28 days total.	CYP450 substrate CYP3A4 and 2B6 inducer **Contraindicated** in patients with moderate to severe hepatic impairment. Dose adjustment is recommended in patients on hemodialysis (see Appendix B, Table 10).	25–30 hours	Rash, including Stevens-Johnson syndrome[d] **Symptomatic Hepatitis:** • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported. • Rash has been reported in approximately 50% of cases. • Symptomatic hepatitis occurs at a significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/mm^3. • NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.
Rilpivirine (RPV) *Edurant*	**Edurant:** • 25 mg tablet **STRs that Contain RPV:**[c] • Complera (RPV/TDF/FTC) • Juluca (DTG/RPV) • Odefsey (RPV/TAF/FTC)	**Edurant:** • RPV 25 mg once daily Take with a meal. See Appendix B, Table 1 for dosing information for STRs that contain RPV.	CYP3A4 substrate	50 hours	Rash[d] Depression, insomnia, headache Hepatotoxicity QT interval prolongation

[a] For dose adjustments in patients with renal or hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 1 for information about these formulations.

[d] Rare cases of Stevens-Johnson syndrome have been reported with the use of most NNRTIs; the highest incidence of rash was seen among patients who were receiving NVP.

[e] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (e.g., suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Key: 3TC = lamivudine; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; FDC = fixed-dose combination; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 1 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Atazanavir (ATV) *Reyataz* (ATV/c) *Evotaz* **Note:** Generic capsule formulations of ATV are available.	**Reyataz:** • 150, 200, and 300 mg capsules • 50 mg single packet oral powder **Evotaz:** • ATV 300 mg/ COBI 150 mg tablet	**Reyataz** *In ARV-Naive Patients:* • (ATV 300 mg plus RTV 100 mg) once daily; *or* • ATV 400 mg once daily • Take with food. *With TDF or in ARV-Experienced Patients:* • (ATV 300 mg plus RTV 100 mg) once daily • Unboosted ATV **is not recommended**. • Take with food. *With EFV in ARV-Naive Patients:* • (ATV 400 mg plus RTV 100 mg) once daily • Take with food. **Evotaz:** • One tablet once daily • Take with food. • The use of ATV/c **is not recommended** for patients who are taking TDF and who have with baseline CrCl <70 mL/min (see Appendix B, Table 10 for the equation for calculating CrCl). For dosing recommendations with H2 antagonists and PPIs, refer to Table 21a	**ATV:** • CYP3A4 inhibitor and substrate • Weak CYP2C8 inhibitor • UGT1A1 inhibitor **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 10).	7 hours	Indirect hyperbilirubinemia PR interval prolongation. First degree symptomatic AV block has been reported. Use with caution in patients who have underlying conduction defects or who are on concomitant medications that can cause PR prolongation. Cholelithiasis Nephrolithiasis Renal insufficiency Serum transaminase elevations Hyperlipidemia (especially with RTV boosting) Skin rash Hyperglycemia Fat maldistribution An increase in serum creatinine may occur when ATV is administered with COBI

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 2 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Darunavir (DRV) *Prezista* (DRV/c) *Prezcobix*	**Prezista:** • 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension **Prezcobix:** • DRV 800 mg/ COBI 150 mg tablet Also available as part of the STR Symtuza (DRV/c/ TAF/FTC)	**Prezista** *In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations:* • (DRV 800 mg plus RTV 100 mg) once daily • Take with food. *In ARV-Experienced Patients with One or More DRV Resistance Mutations:* • (DRV 600 mg plus RTV 100 mg) twice daily • Take with food. Unboosted DRV **is not recommended**. **Prezcobix:** • One tablet once daily • Take with food. • **Not recommended** for patients with one or more DRV resistance-associated mutations. • Coadministering Prezcobix and TDF **is not recommended** for patients with baseline CrCl <70 mL/ min (see Appendix B, Table 10 for the equation for calculating CrCl). See Appendix B, Table 1 for dosing information for Symtuza.	**DRV:** • CYP3A4 inhibitor and substrate • CYP2C9 inducer **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	15 hours when combined with RTV 7 hours when combined with COBI	**Skin Rash:** DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported. Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia Serum transaminase elevation Hyperglycemia Fat maldistribution An increase in serum creatinine may occur when DRV is administered with COBI

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 3 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Fosamprenavir (FPV, a prodrug of APV) *Lexiva* **Note:** Generic is available.	**Lexiva:** • 700 mg tablet • 50 mg/mL oral suspension	*In ARV-Naive Patients:* • FPV 1,400 mg twice daily, *or* • (FPV 1,400 mg plus RTV 100–200 mg) once daily, *or* • (FPV 700 mg plus RTV 100 mg) twice daily *In PI-Experienced Patients:* • (FPV 700 mg plus RTV 100 mg) twice daily • Once-daily dosing **is not recommended** for these patients *In Patients Taking EFV:* • (FPV 700 mg plus RTV 100 mg) twice daily, *or* • (FPV 1,400 mg plus RTV 300 mg) once daily **Food Restrictions** *Without RTV Tablet:* • Take the FPV tablet without regard to meals. *With RTV Tablet:* • Take the RTV tablet and FPV tablet 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 10).	7.7 hours (APV)	Skin rash has been 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*	**Crixivan:** • 200 and 400 mg capsules	**Crixivan:** • IDV 800 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) twice daily • Take without regard to meals. Patients should drink at least 48 ounces of water daily while taking IDV.	CYP3A4 inhibitor and substrate Dose adjustment is recommended in patients with hepatic insufficiency (see Appendix B, Table 10).	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 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 4 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra* **Note:** LPV is only available as a component of an FDC tablet that also contains RTV.	**Kaletra:** • LPV/r 200 mg/50 mg tablets • LPV/r 100 mg/25 mg tablets • LPV/r 400 mg/100 mg per 5 mL of oral solution. Oral solution contains 42% alcohol.	**Kaletra:** • LPV/r 400 mg/100 mg twice daily, *or* • LPV/r 800 mg/200 mg once daily. However, Once-daily dosing **is not recommended** for patients with three or more LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. *With EFV or NVP in PI-Naive or PI-Experienced Patients:* • LPV/r 500 mg/125 mg tablets twice daily (use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or* • LPV/r 533 mg/133 mg oral solution twice daily **Food Restrictions** *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	GI intolerance, nausea, vomiting, diarrhea Pancreatitis Asthenia Hyperlipidemia (especially hypertriglyceridemia) Serum transaminase elevation Hyperglycemia Insulin resistance/diabetes mellitus Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia PR interval prolongation QT interval prolongation and Torsades de Pointes have been reported; however, causality could not be established.
Nelfinavir (NFV) *Viracept*	**Viracept:** • 250 and 625 mg tablets	**Viracept:** • NFV 1,250 mg twice daily, *or* • NFV 750 mg three times a day 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 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 5 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Ritonavir (RTV) *Norvir* **Note:** Generic is available. Although RTV was initially developed as a PI for HIV treatment, RTV is currently used at a lower dose of 100 mg to 200 mg once or twice daily as a PK enhancer to increase the concentrations of other PIs.	**Norvir:** • 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution. Oral solution contains 43% alcohol. • 100 mg single packet oral powder Also available as part of the FDC tablet Kaletra (LPV/r)	**As a PK Booster (or Enhancer) for Other PIs:** • RTV 100–400 mg per day in one or two divided doses (refer to other PIs for specific dosing recommendations). **Food Restrictions** *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 > 2D6 substrate Potent CYP3A4 and 2D6 inhibitor Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	3–5 hours	GI intolerance, nausea, vomiting, diarrhea Paresthesia (circumoral and extremities) Hyperlipidemia (especially hypertriglyceridemia) Hepatitis Asthenia Taste perversion Hyperglycemia Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia
Saquinavir (SQV) *Invirase*	**Invirase:** • 500 mg tablet • 200 mg capsule	**Invirase:** • (SQV 1,000 mg plus RTV 100 mg) twice daily 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. Cases of Torsades de Pointes have been reported. Patients with pre-SQV QT intervals >450 msec should not receive SQV.

Appendix B, Table 5. Characteristics of Protease Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 6 of 6)

Generic Name (Abbreviations) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Adverse Events[b]
Tipranavir (TPV) *Aptivus*	**Aptivus:** • 250 mg capsule • 100 mg/mL oral solution	**Aptivus:** • (TPV 500 mg plus RTV 200 mg) twice daily • Unboosted TPV **is not recommended**. **Food Restrictions** *With RTV Tablets:* • Take with meals. *With RTV Capsules or Solution:* • Take without regard to meals.	CYP3A4 inducer and substrate CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer Net effect of combining TPV and RTV is a CYP3A4 and 2D6 inhibitor	6 hours after single dose of TPV/r	Hepatotoxicity. Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases. Skin rash. TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, and the use of anticoagulant or antiplatelet agents (including vitamin E). Hyperlipidemia Hyperglycemia Fat maldistribution Possible increase in the frequency of bleeding episodes in patients with hemophilia

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10.

[b] Also see Table 17.

Key: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronyl transferase

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Bictegravir (BIC)	BIC is only available as part of the STR Biktarvy (BIC/TAF/FTC).[c]	**Biktarvy:** • One tablet once daily	CYP3A4 substrate UGT1A1-mediated glucuronidation	~17 hours	Diarrhea Nausea Headache
Dolutegravir (DTG) *Tivicay*	**Tivicay:** • 50 mg tablet **STRs that Contain DTG:**[c] • Dovato (DTG/3TC) • Juluca (DTG/RPV) • Triumeq (DTG/ABC/3TC)	*In ARV-Naive or ARV-Experienced, INSTI-Naive Patients:* • DTG 50 mg once daily *In ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Coadministered with EFV, FPV/r, TPV/r, or Rifampin:* • DTG 50 mg twice daily *INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance:* • DTG 50 mg twice daily See Appendix B, Table 1 for dosing information for STRs that contain DTG.	UGT1A1-mediated glucuronidation Minor substrate of CYP3A4	~14 hours	Insomnia Headache Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions) Weight gain Hepatotoxicity Preliminary data suggest an increased rate of neural tube defects in infants born to mothers who were taking DTG at the time of conception. HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury), have been reported.
Elvitegravir (EVG) **Note:** EVG is only available as a component of an FDC tablet that also contains COBI, FTC, and either TDF or TAF.	**STRs that Contain EVG:**[c] • Genvoya (EVG/c/TAF/FTC) • Stribild (EVG/c/TDF/FTC)	**Genvoya:** • One tablet once daily with food • See Appendix B, Table 10 for dosing recommendations in persons with renal insufficiency. **Stribild:** • One tablet once daily with food • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 10 for the equation for calculating CrCl).	**EVG:** • CYP3A and UGT1A1/3 substrate **COBI:** • CYP3A inhibitor and substrate • CYP2D6 inhibitor	~13 hours (EVG/c)	Nausea Diarrhea Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions)

Appendix B, Table 6. Characteristics of Integrase Strand Transfer Inhibitors (Last updated July 10, 2019; last reviewed July 10, 2019) (page 2 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Raltegravir (RAL) *Isentress* *Isentress HD*	**Isentress:** • 400 mg tablet • 25 and 100 mg chewable tablets • 100 mg single packet for oral suspension **Isentress HD:** • 600 mg tablet	**Isentress** *In ARV-Naive Patients or ARV-Experienced Patients:* • 400 mg twice daily *With Rifampin:* • 800 mg twice daily **Isentress HD** *In ARV-Naive or ARV-Experienced Patients with Virologic Suppression on a Regimen of RAL 400 mg Twice Daily:* • 1,200 mg (two 600-mg tablets) once daily *With Rifampin:* • **Not recommended**	UGT1A1-mediated glucuronidation	~9 hours	Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis Nausea Headache Diarrhea Pyrexia CPK elevation, muscle weakness, and rhabdomyolysis Insomnia Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions)

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10. When no food restriction is listed, the ARV drug can be taken with or without food.

[b] Also see Table 17.

[c] See Appendix B, Table 1 for information about these formulations.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate glucuronyl transferase

Appendix B, Table 7. Characteristics of the Fusion Inhibitor (Lasted updated January 29, 2008; last reviewed July 10, 2019)

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

[a] Also see Table 17.

Key: HSR = hypersensitivity reaction; SQ = subcutaneous; T-20 = enfuvirtide

Appendix B, Table 8. Characteristics of the CCR5 Antagonist (Lasted updated March 27, 2012; last reviewed July 10, 2019)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	**Selzentry:** • 150 and 300 mg tablets	**Selzentry:** • MVC 150 mg twice daily when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers), including PIs (except TPV/r) • MVC 300 mg twice daily when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg twice daily when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take MVC without regard to meals.	14–18 hours	CYP3A4 substrate	Abdominal pain Cough Dizziness Musculoskeletal symptoms Pyrexia Rash Upper respiratory tract infections Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions Orthostatic hypotension, especially in patients with severe renal insufficiency

[a] For dose adjustments in patients with hepatic insufficiency, see Appendix B, Table 10.

[b] Also see Table 17.

Key: CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T-20 = enfuvirtide; TPV/r = tipranavir/ritonavir

Appendix B, Table 9. Characteristics of the CD4 Post-Attachment Inhibitor (Last updated July 10, 2019; last reviewed July 10, 2019)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events
Ibalizumab (IBA) *Trogarzo*	**Trogarzo:** • Single-dose 2 mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab	**Trogarzo:** • Administer a single loading dose of IBA 2,000 mg IV infusion over 30 minutes, followed by a maintenance dose of IBA 800 mg IV infusion over 15 minutes every 2 weeks. • See prescribing information for additional instructions for preparing, storing, and administering IBA, and for monitoring patients who are receiving IBA.	~64 hours	Not well defined	Diarrhea Dizziness Nausea Rash

Key: IBA = ibalizumab; IV = intravenous

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (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>
<tr><th>Generic Name
(Abbreviations)
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>
<tr><td colspan="4">NRTIs
Stribild should not be initiated in patients with CrCl <70 mL/min. The following FDC tablets are not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Delstrigo, Dovato, Epzicom, Triumeq, or Trizivir. Biktarvy, Descovy, Odefsey, Symtuza, and Truvada are not recommended in patients with CrCl <30 mL/min.</td></tr>
<tr><td>Abacavir
(ABC)
Ziagen</td><td>ABC 300 mg PO twice daily
or
ABC 600 mg PO once daily</td><td>No dose adjustment necessary.</td><td>Child-Pugh Class A: ABC 200 mg PO twice daily (use oral solution)
Child-Pugh Class B or C:
Contraindicated</td></tr>
<tr><td>Didanosine EC
(ddI)
Videx EC</td><td>Body Weight ≥60 kg:
• ddI 400 mg PO once daily
Body Weight <60 kg:
• ddI 250 mg PO once daily</td><td><table><tr><th colspan="3">Once-Daily Dose by Body Weight</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>125 mg</td></tr><tr><td>10–29</td><td>125 mg</td><td>125 mg</td></tr><tr><td><10, HD,[c] or CAPD</td><td>125 mg</td><td>75 mg oral solution</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
<tr><td>Didanosine Oral Solution
(ddI)
Videx</td><td>Body Weight ≥60 kg:
• ddI 200 mg PO twice daily, or
• ddI 400 mg PO once daily
Body Weight <60 kg:
• ddI 250 mg PO once daily, or
• ddI 125 mg PO twice daily</td><td><table><tr><th colspan="3">Once-Daily Dose by Body Weight</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>150 mg</td></tr><tr><td>10–29</td><td>150 mg</td><td>100 mg</td></tr><tr><td><10, HD,[c] or CAPD</td><td>100 mg</td><td>75 mg</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
<tr><td>Emtricitabine
(FTC)
Emtriva</td><td>FTC 200 mg oral capsule once daily
or
FTC 240 mg (24 mL) oral solution once daily</td><td><table><tr><th colspan="3">Dose by Formulation</th></tr><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg q48h</td><td>120 mg q24h</td></tr><tr><td>15–29</td><td>200 mg q72h</td><td>80 mg q24h</td></tr><tr><td><15 or on HD[c]</td><td>200 mg q96h</td><td>60 mg q24h</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Lamivudine
(3TC)
Epivir</td><td>3TC 300 mg PO once daily
or
3TC 150 mg PO twice daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg q24h</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg q24h</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg q24h</td></tr><tr><td><5 or on HD[c]</td><td>1 x 50 mg, then 25 mg q24h</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
</table>

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 2 of 7)

<table>
<tr><th>Generic Name
(Abbreviations)
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>
<tr><td colspan="4">NRTIs, continued</td></tr>
<tr><td>Stavudine
(d4T)
Zerit</td><td>Body Weight ≥60 kg:
• d4T 40 mg PO twice daily
Body Weight <60 kg:
• d4T 30 mg PO twice daily</td><td><table><tr><th colspan="3">Dose by Body Weight</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>26–50</td><td>20 mg q12h</td><td>15 mg q12h</td></tr><tr><td>10–25 or on HD[c]</td><td>20 mg q24h</td><td>15 mg q24h</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Tenofovir Alafenamide/ Emtricitabine
(TAF/FTC)
Descovy</td><td>TAF for HIV treatment is only available as a component of FDC tablets (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 FDC tablets</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td><30 or on HD[c]</td><td>Not recommended</td></tr></table></td><td>Child-Pugh Class A or B: No dose adjustment
Child-Pugh Class C: No dose recommendation</td></tr>
<tr><td>Tenofovir Disoproxil Fumarate
(TDF)
Viread</td><td>TDF 300 mg PO once daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>300 mg q48h</td></tr><tr><td>10–29</td><td>300 mg twice weekly (q72–96h)</td></tr><tr><td><10 and not on HD</td><td>No recommendation</td></tr><tr><td>On HD[c]</td><td>300 mg q7d</td></tr></table></td><td>No dose adjustment necessary.</td></tr>
<tr><td>Tenofovir Disoproxil Fumarate/ Emtricitabine
(TDF/FTC)
Truvada</td><td>One tablet PO once daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>One tablet q48h</td></tr><tr><td><30 or on HD</td><td>Not recommended</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Tenofovir Disoproxil Fumarate/ Lamivudine
(TDF/3TC)
Cimduo</td><td>One tablet PO once daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td><50 or on HD</td><td>Not recommended</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td>Zidovudine
(ZDV)
Retrovir</td><td>ZDV 300 mg PO twice daily</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td><15 or on HD[c]</td><td>100 mg three times a day or 300 mg once daily</td></tr></table></td><td>No dose recommendation.</td></tr>
<tr><td colspan="4">NNRTIs</td></tr>
<tr><td>Doravirine
(DOR)
Pifeltro</td><td>One tablet PO once daily</td><td>No dose adjustment required in mild, moderate, or severe renal impairment. Has not been studied in ESRD or HD.</td><td>Child-Pugh Class A or B: No dose adjustment
Child-Pugh Class C: Not studied</td></tr>
</table>

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 3 of 7)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
NNRTIs, continued			
Doravirine/ Tenofovir Disoproxil Fumarate/ Lamivudine (DOR/TDF/3TC) *Delstrigo*	One tablet PO once daily	**Not recommended** if CrCl <50 mL/min.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* Not studied
Efavirenz (EFV) *Sustiva*	EFV 600 mg PO once daily on an empty stomach, preferably at bedtime	No dose adjustment necessary.	No dose recommendation; use with caution in patients with hepatic impairment.
Efavirenz/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	One tablet 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.
Efavirenz 600 mg/Tenofovir Disoproxil Fumarate/ Lamivudine (EFV/TDF/3TC) *Symfi*	One tablet once daily on an empty stomach, preferably at bedtime	**Not recommended** if CrCl <50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.	**Not recommended** for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
Efavirenz 400 mg/Tenofovir Disoproxil Fumarate/ Lamivudine (EFV/TDF/3TC) *Symfi Lo*	One tablet once daily on an empty stomach, preferably at bedtime	**Not recommended** if CrCl <50 mL/min or if patient is on HD. Instead, use the individual drugs and adjust TDF and 3TC doses according to CrCl level.	**Not recommended** for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
Etravirine (ETR) *Intelence*	ETR 200 mg PO twice daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	NVP 200 mg PO twice daily *or* NVP 400 mg PO once daily (using Viramune XR formulation)	No dose adjustment for patients with renal impairment. Patients on HD should receive an additional dose of NVP 200 mg following each dialysis treatment.	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B or C:* **Contraindicated**
Rilpivirine (RPV) *Edurant*	RPV 25 mg PO once daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 4 of 7)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
NNRTIs, continued			
Rilpivirine/ Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	One 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*	One 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*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
PIs			
Atazanavir (ATV) *Reyataz*	ATV 400 mg PO once daily *or* (ATV 300 mg plus RTV 100 mg) PO once daily	No dose adjustment for patients with renal dysfunction who do not require HD. *In ARV-Naive Patients on HD:* • (ATV 300 mg plus RTV 100 mg) once daily *In ARV-Experienced Patients on HD:* • ATV and ATV/r a**re not recommended**	*Child-Pugh Class A:* No dose adjustment *Child-Pugh Class B:* ATV 300 mg once daily (unboosted) for ARV-naive patients only *Child-Pugh Class C:* **Not recommended** RTV boosting **is not recommended** in patients with hepatic impairment.
Atazanavir/ Cobicistat (ATV/c) *Evotaz*	One tablet PO once daily	*If Used with TDF:* • **Not recommended** if CrCl <70 mL/min	**Not recommended** in patients with hepatic impairment.
Darunavir (DRV) *Prezista*	*In ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations:* • (DRV 800 mg plus RTV 100 mg) PO once daily with food *In ARV-Experienced Patients with at Least One DRV Resistance Mutation:* • (DRV 600 mg plus RTV 100 mg) PO twice daily	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Impairment:* No dose adjustment *In Patients with Severe Hepatic Impairment:* **Not recommended**
Darunavir/ Cobicistat (DRV/c) *Prezcobix*	One tablet PO once daily	*If Used with TDF:* • **Not recommended** if CrCl <70 mL/min	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 5 of 7)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
PIs, continued			
Darunavir/ Cobicistat/ Tenofovir Alafenamide/ Emtricitabine (DRV/c/TAF/FTC) *Symtuza*	One tablet PO once daily	**Not recommended** if CrCl <30 mL/min.	**Not recommended** for patients with severe hepatic impairment.
Fosamprenavir (FPV) *Lexiva*	1,400 mg PO twice daily *or* (FPV 1,400 mg plus RTV 100–200 mg) PO once daily *or* (FPV 700 mg plus RTV 100 mg) PO twice daily	No dose adjustment necessary.	**In PI-Naive Patients Only (without RTV)** *Child-Pugh Score 5–9:* • FPV 700 mg twice daily *Child-Pugh Score 10–15:* • FPV 350 mg twice daily **In PI-Naive or PI-Experienced Patients** *Child-Pugh Score 5–6:* • FPV 700 mg twice daily plus RTV 100 mg once daily *Child-Pugh Score 7–9:* • FPV 450 mg twice daily plus RTV 100 mg once daily *Child-Pugh Score 10–15:* • FPV 300 mg twice daily plus RTV 100 mg once daily
Indinavir (IDV) *Crixivan*	IDV 800 mg PO q8h	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Insufficiency Due to Cirrhosis:* IDV 600 mg q8h
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	(LPV/r 400 mg/100 mg) PO twice daily *or* (LPV/r 800 mg/200 mg) PO once daily	Avoid once-daily dosing in patients on HD.	No dose recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV) *Viracept*	NFV 1,250 mg PO twice daily	No dose adjustment necessary.	*In Patients with Mild Hepatic Impairment:* No dose adjustment *In Patients with Moderate-to-Severe Hepatic Impairment:* **Not recommended**
Ritonavir (RTV) *Norvir*	*As a PI-Boosting Agent:* • RTV 100–400 mg per day	No dose adjustment necessary.	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	(SQV 1,000 mg plus RTV 100 mg) PO twice daily	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Impairment:* Use with caution *In Patients with Severe Hepatic Impairment:* **Contraindicated**

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 6 of 7)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
PIs, continued			
Tipranavir (TPV) *Aptivus*	(TPV 500 mg plus RTV 200 mg) PO twice daily	No dose adjustment necessary.	*Child-Pugh Class A:* Use with caution *Child-Pugh Class B or C:* **Contraindicated**
INSTIs			
Bictegravir/ Tenofovir Alafenamide/ Emtricitabine (BIC/TAF/FTC) *Biktarvy*	One tablet once daily	**Not recommended** for use in patients with CrCl <30 mL/min.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir (DTG) *Tivicay*	DTG 50 mg once daily *or* DTG 50 mg twice daily	No dose adjustment necessary.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* **Not recommended**
Dolutegravir/ Abacavir/ Lamivudine (DTG/ABC/3TC) *Triumeq*	One tablet once daily	Not recommended if CrCl <50 mL/min. Instead, use the individual drugs and adjust 3TC dose according to CrCl.	*Child-Pugh Class A:* Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these patients. *Child-Pugh Class B or C:* **Contraindicated** due to the ABC component
Dolutegravir/ Rilpivirine (DTG/RPV) *Juluca*	One tablet PO once daily with food	No dose adjustment necessary. In patients with CrCl <30 mL/min, monitor closely for adverse effects.	*Child-Pugh Class A or B:* No dose adjustment *Child-Pugh Class C:* No dose recommendation
Elvitegravir/ Cobicistat/ Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	One tablet once daily	*In Patients on Chronic HD:* • One tablet once daily. On dialysis days, administer after dialysis. **Not recommended** in patients with CrCl <30 mL/min or ≤15 mL/min who are not receiving chronic HD.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* **Not recommended**
Elvitegravir/ Cobicistat/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EVG/c/TDF/FTC) *Stribild*	One tablet once daily	EVG/c/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* **Not recommended**
Raltegravir (RAL) *Isentress* *Isentress HD*	RAL 400 mg twice daily (using Isentress formulation) *or* RAL 1,200 mg once daily (using Isentress HD formulation only)	No dose adjustment necessary.	*In Patients with Mild-to-Moderate Hepatic Insufficiency:* No dose adjustment necessary *In Patients with Severe Hepatic Insufficiency:* No recommendation

Appendix B, Table 10. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 10, 2019; last reviewed July 10, 2019) (page 7 of 7)

Generic Name (Abbreviations) *Trade Name*	Usual Daily Dose[a]	Dosing in Patients with Renal Insufficiency[b]	Dosing in Patients with Hepatic Impairment
Fusion Inhibitor			
Enfuvirtide (T-20) *Fuzeon*	T-20 90 mg SQ twice daily	No dose adjustment necessary.	No dose adjustment necessary.
CCR5 Antagonist			
Maraviroc (MVC) *Selzentry*	The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 8 for detailed dosing information.	*In Patients with CrCl <30 mL/min or Patients Who Are on HD* Without Potent CYP3A Inhibitors or Inducers: • MVC 300 mg twice daily; reduce to 150 mg twice daily 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 IBA 2,000 mg IV, followed by a maintenance dose of IBA 800 mg IV every 2 weeks	No dose adjustment recommended.	No recommendation.

[a] Refer to Appendix B, Tables 1–9 for additional dosing information.

[b] Including patients who are on CAPD and HD.

[c] On dialysis days, the patient should take the dose after the HD session.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CAPD = chronic ambulatory peritoneal dialysis; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ESRD = end stage renal disease; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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 = nelfinavir; 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; SQ = subcutaneous; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; XR = extended release; ZDV = zidovudine

Creatinine Clearance Calculation			
Male:	$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	Female:	$\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy[a]	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin, *or*	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34–50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified total bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged), *or*	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

[a] **Encephalopathy Grades**

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score