Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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

How to Cite the Adult and Adolescent Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

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

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What's New in the Guidelines? (Last updated July 14, 2016; last reviewed July 14, 2016)

Revisions to the January 28, 2016, version of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* include key updates to several sections. Significant updates are highlighted throughout the document.

Key Updates

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient

The approval of 3 fixed-dose combination products containing tenofovir alafenamide (an oral prodrug of tenofovir) and emtricitabine (TAF/FTC) prompted several changes in the What to Start section. The key changes are highlighted below:

- TAF/FTC was added as a 2-NRTI option in several Recommended and Alternative regimens, as noted in Table 6 of the guidelines. The addition of TAF/FTC to these recommendations is based on data from comparative trials demonstrating that TAF-containing regimens are as effective in achieving or maintaining virologic suppression as tenofovir disoproxil fumarate (TDF)-containing regimens and with more favorable effects on markers of bone and renal health.
- In the What to Start section, the evidence quality rating "II" was expanded to include "relative bioavailability/bioequivalence studies or regimen comparisons from randomized switch studies." This evidence rating was broadened because not all recommended regimens were evaluated in randomized, controlled trials in antiretroviral therapy (ART)-naive patients. The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) based their recommendations for some regimens on either data from bioequivalence or relative bioavailability studies, or by extrapolating results from randomized "switch" studies that evaluated a drug's or regimen's ability to maintain virologic suppression in patients whose HIV was suppressed on a previous regimen. Guidance for clinicians on choosing between abacavir (ABC)-, TAF-, and TDF-containing regimens was added to What to Start.
- The lopinavir/ritonavir (LPV/r) plus 2-NRTI regimen was removed from the list of Other regimens because regimens containing this protease inhibitor (PI) combination have a larger pill burden and greater toxicity than other currently available options.

Regimen Switching

- Based on the most current data, this section was simplified to focus on switch strategies for virologically suppressed patients. The strategies are categorized as Strategies with Good Supporting Evidence, Strategies Under Evaluation, and Strategies Not Recommended.

HIV-Infected Women

- The Panel emphasizes that ART is recommended for all HIV-infected patients, including all HIV-infected women.
- The Panel also stresses the importance of early treatment for HIV-infected women during pregnancy and continuation of ART after pregnancy.
- This section was updated to include new data on interactions between antiretroviral (ARV) drugs and hormonal contraceptives.

Hepatitis B Virus (HBV)/HIV Coinfection

- This section was updated to include TAF/FTC as a treatment option for patients with HBV/HIV

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coinfection. Data on the virologic efficacy of TAF for the treatment of HBV in persons without HIV infection and TAF/FTC in persons with HBV/HIV coinfection are discussed.

- The Panel no longer recommends adefovir or telbivudine as options for HBV/HIV coinfected patients, as there is limited safety and efficacy data on their use in this population. In addition, these agents have a higher incidence of toxicities than other recommended treatments.

Hepatitis C Virus (HCV)/HIV Coinfection

- The text and Table 12 in this section were updated with information regarding the potential pharmacokinetic (PK) interactions between different ARV drugs and the recently approved hepatitis C drugs daclatasvir and the fixed-dose combination product of elbasvir and grazoprevir.
- Peginterferon alfa and ribavirin were removed from Table 12, as these agents do not have significant PK interactions with ARV drugs.

Tuberculosis (TB)/HIV Coinfection

- This section was updated to include a discussion on the treatment of latent tuberculosis infection (LTBI) in HIV-infected persons. The added discussion notes that a 12-week course of once-weekly rifapentine and isoniazid is an option for patients receiving either an efavirenz (EFV)- or a raltegravir (RAL)-based regimen.
- This section addresses the data from the TEMPRANO and START studies demonstrating a potential role of ART in reducing TB disease.
- The recommendations and discussion regarding when to initiate ART in patients with active TB were simplified.
- As rifamycins are potent inducers of P-glycoprotein (P-gp), and TAF is a P-gp substrate, coadministration of TAF and rifamycins is not recommended.

Additional Updates

Minor revisions were made to the following sections:

- Laboratory Testing for Initial Assessment and Monitoring of HIV-Infected Patients on Antiretroviral Therapy
- Drug Resistance Testing
- Adverse Effects of Antiretroviral Agents and Tables 14 and 15
- Monthly Average Wholesale Price of Commonly Used Antiretroviral Drugs (Table 16)
- Drug Interaction Tables 18, 19a-e, and 20b
- Drug Characteristics Tables (Appendix B, Tables 1–7)

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HHS Panel on Antiretroviral Guidelines for Adults and Adolescents
Panel Roster (Last updated July 14, 2016; last reviewed July 14, 2016)

These Guidelines were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Research Advisory Council).

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Tim Horn	Treatment Action Group, New York NY
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Andy Kaytes	AIDS Treatment Activists Coalition, San Diego, CA
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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2015 to February 2016) (page 1 of 4)

Panel Member	Status	Company	Relationship
Judith Aberg	M	• Bristol-Myers Squibb • Gilead • Janssen • Merck • ViiV	• Research support • Research support • Advisory Board • Advisory Board • Advisory Board
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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2015 to February 2016) (page 2 of 4)

Panel Member	Status	Company	Relationship
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H. Clifford Lane	C	None	N/A
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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2015 to February 2016) (page 3 of 4)

Panel Member	Status	Company	Relationship
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Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents Financial Disclosure (Reporting Period: February 2015 to February 2016) (page 3 of 4)

Panel Member	Status	Company	Relationship
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Nelson R. Vergel (Term completed April 2016)	M	None	N/A
Rochelle Walensky	M	None	N/A

Key to Abbreviations: C = Co-Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; M = Member; N/A = Not Applicable

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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, fewer than one-third of HIV-infected individuals 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 (ARV) used to treat adults and adolescents with HIV infection 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 post-pubertal adolescents (i.e., sexual maturity rating [SMR] stages IV and V). Clinicians should follow recommendations in the Pediatric Guidelines when initiating ART in adolescents at SMR stage III or lower.[3] For recommendations related to pre- (PrEP) and post- (PEP) HIV exposure prophylaxis for HIV uninfected persons, 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.

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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 infection 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 and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are non-governmental 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 ART use for HIV-infected adults and adolescents. For more detailed discussion on the use of antiretroviral therapy (ART) for children and pre-pubertal adolescents (SMR Stages I – III), clinicians should refer to the Pediatric Antiretroviral Guidelines. These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women.
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.

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Basis for Recommendations

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

Table 2. Rating Scheme for Recommendations

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

HIV Expertise in Clinical Care

Several studies have demonstrated that overall outcomes in HIV-infected patients 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 infection and its treatment. Appropriate training, continuing education, and clinical experience are all components of optimal care. Providers who do not have this requisite training and experience should consult HIV experts when needed.

References

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.
2. Centers for Disease Control and Prevention. HIV in the United States: the stages of care—CDC Fact Sheet. 2014. Available at http://www.cdc.gov/nchhstp/newsroom/docs/HIV-Stages-of-Care-Factsheet-508.pdf. Accessed December 21, 2015.
3. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed January 12, 2016.
4. Centers for Disease Control and Prevention, U.S. Public Health Service. Pre-exposure prophylaxis for the prevention of HIV infection in the United States—2014: a clinical practice guideline. 2014. Available at http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf. Accessed November 2, 2015.
5. Kitahata MM, Van Rompaey SE, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Syndr*. Jun 1 2000;24(2):106-114. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10935685.
6. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med*. May 23 2005;165(10):1133-1139. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15911726.
7. Kitahata MM, Van Rompaey SE, Dillingham PW, et al. Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS. *J Gen Intern Med*. Feb 2003;18(2):95-103. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12542583.
8. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. *Antivir Ther*. Oct 2003;8(5):471-478. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14640395.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

9. O'Neill M, Karelas GD, Feller DJ, et al. The HIV Workforce in New York State: Does Patient Volume Correlate with Quality? *Clin Infect Dis*. Dec 15 2015;61(12):1871-1877. Available at http://www.ncbi.nlm.nih.gov/pubmed/26423383.

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

Every HIV-infected patient 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 introductory 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-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 at entry into care, regardless of whether ART will be initiated immediately **(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 (see Preventing Secondary Transmission of HIV).

References

1. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;58(1):e1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24235263.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 6, 2014.

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Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring of HIV-Infected Patients on Antiretroviral Therapy (Last updated July 14, 2016; last reviewed July 14, 2016)

A number of laboratory tests are important for initial evaluation of HIV-infected patients upon entry into care, and 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 HIV-infected patients: CD4 T lymphocyte 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. Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART, as treatment of these coinfections may affect the choice of ART. The rationale for and utility of these laboratory tests are discussed in the corresponding sections of the guidelines.

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Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 2)

Laboratory Test	Timepoint/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 on ART or CD4 count <300 cells/mm^3		√ After 2 years on ART with Consistently Suppressed Viral Load: *CD4 Count 300–500 cells/mm^3:* • Every 12 months *CD4 Count >500 cells/mm^3:* • CD4 monitoring is optional	√	√	√ Every 3-6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional
Resistance Testing	√	√[f]					√	√	√[f]
HLA-B*5701 Testing		√ If considering ABC							
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√	

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

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Hepatitis B Serology[g,h]	√	√ May repeat if patient is nonimmune and not chronically infected with HBV[h]				√ May repeat if patient is nonimmune and not chronically infected with HBV[h]		√	
Hepatitis C Antibody Test (if positive, confirm with HCV RNA test)	√	√ May repeat for at-risk patients if negative result at baseline				√ May repeat for at-risk patients if negative result at baseline		√	
Basic Chemistry[i,j]	√	√	√	√				√	√ Every 6-12 months
ALT, AST, T. bilirubin	√	√	√	√				√	√ Every 6-12 months
CBC with Differential	√	√	√ If on ZDV	√ If on ZDV or if CD4 testing is done	√			√	√ Every 3-6 months
Fasting Lipid Profile[k]	√	√			√ 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[j,l]	√	√			√ If on TAF or TDF[l]	√		√	
Pregnancy Test		√ In women with child-bearing potential						√	

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[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 HIV-infected individuals 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 every 4 to 8 weeks until viral load is suppressed to <200 copies/mL, and thereafter, 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 (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (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 virologically suppressed patients 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 HBsAg is positive, TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. Preliminary data from clinical trials have demonstrated TAF activity against HBV. Final results from ongoing clinical trials will help to define the role of TAF in the treatment of HBV/HIV coinfection.

[h] If HBsAg, HBsAb, and anti-HBc are negative, hepatitis B vaccine series should be administered. Refer to HIV Primary Care and Opportunistic Infections guidelines for more detailed recommendations.[1,2]

[i] 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]

[j] 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).

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

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Cl = chloride; CrCl = creatinine clearance; EFV = efavirenz; FTC = emtricitabine; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCO_3 = bicarbonate; K = potassium; NA = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):e1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24235263.
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed June 6, 2016.
3. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Nov 1 2014;59(9):e96-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/25234519.
4. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol*. Mar-Apr 2015;9(2):129-169. Available at http://www.ncbi.nlm.nih.gov/pubmed/25911072.

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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 an HIV-infected patient. 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 HIV-infected patients 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 HIV-infected patients regardless of their viral load or CD4 count. 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 HIV-infected patients 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 HIV-infected patients 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 co-infection 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

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

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

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in HIV-infected patients. 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, is more expensive, and 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 in Antiretroviral-Naive Patients 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] or at an older age[17] may have a blunted increase in their counts despite virologic suppression.

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Frequency of CD4 Count Monitoring

ART is now recommended for all HIV-infected patients. 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.[18] 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.[19] 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.[20] 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.[21] 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.[22]

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 anti-neoplastic 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 section).

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[23,24] or co-infection with human T-lymphotropic virus type I (HTLV-1)[25] may cause misleadingly elevated CD4 counts. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage.[26] In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

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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 **(AIII)**.[b]
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 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 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 and Suboptimal Immunologic Response section)	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.

References

1. Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS*. 1999;13(7):797-804. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10357378.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

2. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis*. 1998;177(1):40-47. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9419168.
3. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al, with the Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA). Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. *AIDS*. 2000;14(8):971-978. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10853978.
4. Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. HIV Surrogate Marker Collaborative Group. *AIDS Res Hum Retroviruses*. 2000;16(12):1123-1133. Available at http://www.ncbi.nlm.nih.gov/pubmed/10954887.
5. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA*. 2001;286(2):171-179. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11448280.
6. Damond F, Roquebert B, Benard A, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche COBAS AMPLICOR HIV-1 MONITOR Version 1.5 and the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assays. *J Clin Microbiol*. 2007;45(10):3436-3438. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17715371.
7. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis*. 2009;48(2):260-262. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19113986.
8. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr*. 2010;54(4):442-444. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20611035.
9. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. 2013;57(10):1489-1496. Available at http://www.ncbi.nlm.nih.gov/pubmed/23946221.
10. Ribaudo H, Lennox J, Currier J, et al. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infection; 2009; Montreal, Canada.
11. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126(12):946-954. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9182471.
12. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. 2002;360(9327):119-129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126821.
13. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 6, 2014.
14. Mocroft A, Furrer HJ, Miro JM, et al. The incidence of AIDS-defining illnesses at a current CD4 count >/= 200 cells/muL in the post-combination antiretroviral therapy era. *Clin Infect Dis*. 2013;57(7):1038-1047. Available at http://www.ncbi.nlm.nih.gov/pubmed/23921881.
15. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med*. 2003;163(18):2187-2195. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14557216.
16. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205456.

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17. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. 2010;24(16):2469-2479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20829678.
18. Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/muL and HIV-1 suppression? *Clin Infect Dis*. 2013;56(9):1340-1343. Available at http://www.ncbi.nlm.nih.gov/pubmed/23315315.
19. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS*. 2013;27(17):2759-2763. Available at http://www.ncbi.nlm.nih.gov/pubmed/23842127.
20. Costiniuk CT, Fergusson DA, Doucette S, Angel JB. Discontinuation of *Pneumocystis jirovecii* pneumonia prophylaxis with CD4 count <200 cells/microL and virologic suppression: a systematic review. *PLoS One*. 2011;6(12):e28570. Available at http://www.ncbi.nlm.nih.gov/pubmed/22194853.
21. Helleberg M, Kronborg G, Larsen CS, et al. CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis*. 2013;57(2):314-321. Available at http://www.ncbi.nlm.nih.gov/pubmed/23575194.
22. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. 2013;173(18):1746-1748. Available at http://www.ncbi.nlm.nih.gov/pubmed/23978894.
23. Zurlo JJ, Wood L, Gaglione MM, Polis MA. Effect of splenectomy on T lymphocyte subsets in patients infected with the human immunodeficiency virus. *Clin Infect Dis*. 1995;20(4):768-771. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7795071.
24. Bernard NF, Chernoff DN, Tsoukas CM. Effect of splenectomy on T-cell subsets and plasma HIV viral titers in HIV-infected patients. *J Hum Virol*. 1998;1(5):338-345. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10195261.
25. Casseb J, Posada-Vergara MP, Montanheiro P, et al. T CD4+ cells count among patients co-infected with human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1): high prevalence of tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). *Rev Inst Med Trop Sao Paulo*. 2007;49(4):231-233. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17823752.
26. Berglund O, Engman K, Ehrnst A, et al. Combined treatment of symptomatic human immunodeficiency virus type 1 infection with native interferon-alpha and zidovudine. *J Infect Dis*. 1991;163(4):710-715. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1672701.

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Drug-Resistance Testing (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations
For Antiretroviral Therapy-Naive Patients:
• HIV drug-resistance testing is recommended for persons with HIV infection at entry into care 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 testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**.
• In special circumstances (e.g., in patients with acute or recent [early] HIV infection and in pregnant HIV-infected women, 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 INSTI genotype testing **(BIII)**.
For Antiretroviral Therapy-Experienced Patients:

• HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ART regimens in the following patients:
  • In patients with virologic failure and HIV RNA levels >1000 copies/mL **(AI)**.
  • In patients with HIV RNA levels >500 copies/mL but <1000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered **(BII)**.
  • Drug-resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**.

• When a patient experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance 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 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 **(CIII)**.
• Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic response or virologic failure while on first- or second-line regimens **(AII)**.
• The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns **(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*

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. Clinicians should check 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. Co-receptor tropism assays should be performed when considering the use of a CCR5 antagonist. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available (see Co-receptor Tropism Assays).

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes. Most genotypic assays involve sequencing the reverse transcriptase (RT), protease (PR), and integrase (IN) genes to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene

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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 (see http://www.iasusa.org/resistance_mutations).[1] The Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu) also provides helpful guidance for interpreting genotypic resistance test results. Various tools to assist the provider in interpreting genotypic test results are now available.[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.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope 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 is 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 are now available 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 less than 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 drugs that exert selective pressure on drug-resistant populations are discontinued. As a consequence, the proportion of virus with resistance mutations decreases 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 before or within 4 weeks after drugs are discontinued **(AII)**. Because resistant virus may persist longer in the plasma of some patients, resistance testing done 4 to 6 weeks after discontinuation of drugs may still detect mutations. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens.

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 antiretroviral therapy (ART).[16-19] The risk of acquiring drug-resistant virus is related to the

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prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in a given community. In high-income countries (e.g., the United States, some European countries, Australia, and Japan), approximately 10% to 17% of ART-naive patients have resistance mutations to at least 1 ARV drug.[20] Up to 8%, but generally less than 5%, of transmitted viruses will exhibit resistance to drugs from more than 1 class.[20-23] Transmitted resistant HIV is generally either NRTI- or NNRTI-resistant. PI resistance is much less common, and to date, transmitted INSTI resistance is rare.[24]

In persons with acute or recent (early) HIV infection, resistance testing can guide therapy selection to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AII)**. A genotypic assay is preferred for this purpose **(AIII)**. In this setting, treatment initiation should not be delayed pending resistance testing results if the patient is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see 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.[25-27] Therefore, if ART is deferred, resistance testing should still be performed during acute HIV infection **(AIII)**. In this situation, the genotypic resistance test result may be kept on record until the patient begins ART. Repeat resistance testing at the start of treatment may be considered because a patient may acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART **(CIII)**.

Interpretation of drug-resistance testing before ART initiation in patients with chronic HIV infection 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.[28-30] No prospective trial has addressed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several studies suggest that virologic responses in persons with baseline resistance mutations are suboptimal.[16-19,31-33] In addition, an analysis of early genotypic resistance testing in treatment-naive HIV-infected patients suggests that baseline testing in this population is cost effective and should be performed.[34] Therefore, resistance testing in chronically infected persons 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 to interpret test results **(AIII)**. If therapy is deferred, repeat testing shortly before initiating ART may be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

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

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 assessed the utility of resistance testing to guide ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6,35-41] In general, these studies found that changes in therapy based on resistance testing 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 performance of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[42] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV

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regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see 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)**. Drug-resistance testing in persons with a plasma viral load <500 copies/mL is not usually recommended because resistance assays cannot be consistently performed given 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 combination ART is, for certain patients, associated with resistance to only one component of the regimen.[43-45] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotypic testing is generally preferred for resistance testing in patients who are on a failing first or second ARV drug regimen and experiencing virologic failure or suboptimal viral load reduction **(AII)**. 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.[46] In patients failing 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)**.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)**. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing, but current data suggest that genotypic tropism testing should be considered as an alternative phenotypic tropism testing. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist.[47] Resistance to CCR5 antagonists in the absence of detectable CXCR4-using virus has been reported, but such resistance is uncommon (see Co-receptor Tropism Assays).

A next-generation sequencing genotypic resistance assay, which analyzes HIV-1 pro-viral DNA in the host cells, is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection. However, the clinical utility of this assay has yet to be determined.

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to 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 women 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 initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

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

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute (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)**. If ART is deferred, repeat resistance testing may be considered when therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified 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. 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 infection: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART **(AII)**. A genotypic assay is generally preferred **(AIII)**. If an INSTI is considered for an ART-naive patient **and** transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay **(BIII)**. If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred **(AIII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).	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. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients. 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. 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.
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)**. A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**. When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**. If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays). Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	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. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy. 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. 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). Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns, particularly to PIs.

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

Clinical Setting/Recommendation	Rationale
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 and thus help the clinician identify the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of 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.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued **(BIII)**.	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

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

References

1. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. Jul 15 2008;47(2):266-285. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18549313.
2. Flandre P, Costagliola D. On the comparison of artificial network and interpretation systems based on genotype resistance mutations in HIV-1-infected patients. *AIDS*. Oct 24 2006;20(16):2118-2120. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17053360.
3. Vercauteren J, Vandamme AM. Algorithms for the interpretation of HIV-1 genotypic drug resistance information. *Antiviral Res*. Sep 2006;71(2-3):335-342. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16782210.
4. Gianotti N, Mondino V, Rossi MC, et al. Comparison of a rule-based algorithm with a phenotype-based algorithm for the interpretation of HIV genotypes in guiding salvage regimens in HIV-infected patients by a randomized clinical trial: the mutations and salvage study. *Clin Infect Dis*. May 15 2006;42(10):1470-1480. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16619162.
5. Torti C, Quiros-Roldan E, Regazzi M, et al. A randomized controlled trial to evaluate antiretroviral salvage therapy guided by rules-based or phenotype-driven HIV-1 genotypic drug-resistance interpretation with or without concentration-controlled intervention: the Resistance and Dosage Adapted Regimens (RADAR) study. *Clin Infect Dis*. Jun 15 2005;40(12):1828-1836. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15909273.
6. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS*. Jan 25 2002;16(2):209-218. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11807305.
7. Lanier ER, Ait-Khaled M, Scott J, et al. Antiviral efficacy of abacavir in antiretroviral therapy-experienced adults harbouring HIV-1 with specific patterns of resistance to nucleoside reverse transcriptase inhibitors. *Antivir Ther*. Feb

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2004;9(1):37-45. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15040535.

8. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis*. Mar 1 2004;189(5):837-846. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14976601.
9. Flandre P, Chappey C, Marcelin AG, et al. Phenotypic susceptibility to didanosine is associated with antiviral activity in treatment-experienced patients with HIV-1 infection. *J Infect Dis*. Feb 1 2007;195(3):392-398. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205478.
10. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. *AIDS*. Jan 11 2007;21(2):179-185. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17197808.
11. Naeger LK, Struble KA. Effect of baseline protease genotype and phenotype on HIV response to atazanavir/ritonavir in treatment-experienced patients. *AIDS*. Apr 4 2006;20(6):847-853. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16549968.
12. Verhofstede C, Wanzeele FV, Van Der Gucht B, De Cabooter N, Plum J. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS*. Dec 24 1999;13(18):2541-2546. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630523.
13. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. Dec 22 2000;14(18):2857-2867. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153667.
14. Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS*. Dec 24 1999;13(18):F123-127. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630517.
15. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis*. Nov 1 2006;194(9):1309-1318. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17041858.
16. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med*. Aug 8 2002;347(6):385-394. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12167680.
17. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses*. Aug 2007;23(8):988-995. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17725415.
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr*. Dec 15 2006;43(5):535-540. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17057609.
19. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis*. Mar 15 2008;197(6):867-870. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18269317.
20. World Health Organization. WHO HIV Drug Resistance Report 2012. Geneva, Switzerland. Available at http://www.who.int/hiv/pub/drugresistance/report2012. Accessed May 13, 2016.
21. Yanik EL, Napravnik S, Hurt CB, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. *J Acquir Immune Defic Syndr*. Oct 1 2012;61(2):258-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/22692092.
22. Agwu AL, Bethel J, Hightow-Weidman LB, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. *AIDS Patient Care STDS*. Apr 2012;26(4):193-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22563607.
23. Castor D, Low A, Evering T, et al. Transmitted drug resistance and phylogenetic relationships among acute and early

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HIV-1-infected individuals in New York City. *J Acquir Immune Defic Syndr*. Sep 1 2012;61(1):1-8. Available at http://www.ncbi.nlm.nih.gov/pubmed/22592583.

24. Doyle T, Dunn DT, Ceccherini-Silberstein F, et al. Integrase inhibitor (INI) genotypic resistance in treatment-naive and raltegravir-experienced patients infected with diverse HIV-1 clades. *J Antimicrob Chemother*. Nov 2015;70(11):3080-3086. Available at http://www.ncbi.nlm.nih.gov/pubmed/26311843.
25. Johnson JA, Li JF, Wei X, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. *PLoS Med*. Jul 29 2008;5(7):e158. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18666824.
26. Simen BB, Simons JF, Hullsiek KH, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. *J Infect Dis*. Mar 1 2009;199(5):693-701. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19210162.
27. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. Mar 2010;201(5):662-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20102271.
28. Smith DM, Wong JK, Shao H, et al. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *J Infect Dis*. Aug 1 2007;196(3):356-360. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597449.
29. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis*. Feb 1 2005;40(3):468-474. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15668873.
30. Little SJ, Frost SD, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol*. Jun 2008;82(11):5510-5518. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18353964.
31. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*. Jul 14 2004;292(2):180-189. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15249567.
32. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med*. Jul 15 2004;351(3):229-240. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15247339.
33. Pillay D, Bhaskaran K, Jurriaans S, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. *AIDS*. Jan 2 2006;20(1):21-28. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327315.
34. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis*. Nov 1 2005;41(9):1316-1323. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16206108.
35. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS*. Feb 15 2002;16(3):369-379. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11834948.
36. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet*. Jun 26 1999;353(9171):2195-2199. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10392984.
37. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS*. 2000;14(9):F83-93. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10894268&dopt=Abstract.
38. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS*. Mar 8 2002;16(4):579-588. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11873001.
39. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral

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therapy after treatment failure: a randomized trial. *AIDS*. Mar 29 2002;16(5):727-736. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11964529.

40. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of care (Narval trial, ANRS 088). *Antivir Ther*. Oct 2003;8(5):427-434. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14640390.
41. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis*. Mar 1 2004;38(5):723-730. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14986258.
42. Palella FJ, Jr., Armon C, Buchacz K, et al. The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study. *Ann Intern Med*. Jul 21 2009;151(2):73-84. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19620160.
43. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. Jan 12 2000;283(2):229-234. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634339.
44. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072 Study Team). *JAMA*. Jan 12 2000;283(2):205-211. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634336.
45. Machouf N, Thomas R, Nguyen VK, et al. Effects of drug resistance on viral load in patients failing antiretroviral therapy. *J Med Virol*. May 2006;78(5):608-613. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16555280.
46. Anderson JA, Jiang H, Ding X, et al. Genotypic susceptibility scores and HIV type 1 RNA responses in treatment-experienced subjects with HIV type 1 infection. *AIDS Res Hum Retroviruse*s. May 2008;24(5):685-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/18462083.
47. Lewis M MJ, Simpson P, et al. Changes in V3 loop sequence associated with failure of maraviroc treatment in patients enrolled in the MOTIVATE 1 and 2 trials. Presented at: 15th Conference on Retroviruses and Opportunistic Infections. 2008. Boston, Massachusetts.

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Co-Receptor Tropism Assays (Last updated February 12, 2013; last reviewed February 12, 2013)

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 also 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)**.
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 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, to a lesser degree, genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., CCR5, CXCR4, or both) 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, a genotypic assay to predict co-receptor usage is now 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. Viruses in many untreated patients eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts,[3, 4] but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.[1] Antiretroviral (ARV)-treated patients with extensive drug resistance are more likely to harbor X4- or D/M-tropic variants than untreated patients with comparable CD4 counts.[5] The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.[5, 6]

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.[7, 8] 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 pre-marketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the *Trofile* assay.[8] 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 CXCR4-utilizing virus at baseline that were below the assay limit of detection and exhibited rapid virologic failure after initiation of a CCR5 antagonist.[9] The assay has been revised 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.[10] Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear

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reasons, a minority of samples cannot be successfully phenotyped with either generation of the *Trofile* assay.

In patients with plasma HIV-1 RNA below the limit of detection, co-receptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined.[11]

Genotypic Assays

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 *env*, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant.[12]

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.[13-15] On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing to determine co-receptor usage.[16] An important caveat to these results 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.

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)**. 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 also may 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 usefulness. Therefore, a phenotypic test for co-receptor usage is generally preferred **(AI)**. However, because phenotypic testing is more expensive and requires more time to perform, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII)**.

A tropism assay may potentially be used in clinical practice for prognostic purposes or to assess tropism before starting ART if future use of a CCR5 antagonist is anticipated (e.g., a regimen change for toxicity). Currently, sufficient data do not exist to support these uses.

References

1. Moore JP, Kitchen SG, Pugach P, Zack JA. The CCR5 and CXCR4 coreceptors—central to understanding the transmission and pathogenesis of human immunodeficiency virus type 1 infection. *AIDS Res Hum Retroviruses*. 2004;20(1):111-126. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15000703.
2. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Med*. 2005;11(11):1170-1172. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16205738.
3. Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use correlates with disease progression in HIV-1-infected individuals. *J Exp Med*. 1997;185(4):621-628. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9034141.
4. Koot M, Keet IP, Vos AH, et al. Prognostic value of HIV-1 syncytium-inducing phenotype for rate of CD4+ cell depletion and progression to AIDS. *Ann Intern Med*. 1993;118(9):681-688. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8096374.

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5. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis*. 2006;194(7):926-930. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16960780.
6. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis*. 2007;44(4):591-595. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17243065.
7. Trouplin V, Salvatori F, Cappello F, et al. Determination of coreceptor usage of human immunodeficiency virus type 1 from patient plasma samples by using a recombinant phenotypic assay. *J Virol*. 2001;75(1):251-259. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11119595.
8. Whitcomb JM, Huang W, Fransen S, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. *Antimicrob Agents Chemother*. 2007;51(2):566-575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17116663.
9. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. *J Virol*. 2006;80(10):4909-4920. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16641282.
10. Trinh L, Han D, Huang W, et al. Technical validation of an enhanced sensitivity Trofile HIV coreceptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5. *Antivir Ther*. 2008;13(Suppl 3):A128
11. Toma J, Frantzell A, Cook J, et al. Phenotypic determination of HIV-1 coreceptor tropism using cell-associated DNA derived from blood samples. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; 2010; San Francisco, CA.
12. Lin NH, Kuritzkes DR. Tropism testing in the clinical management of HIV-1 infection. *Curr Opin HIV AIDS*. 2009;4(6):481-487. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20048714.
13. McGovern RA, Thielen A, Mo T, et al. Population-based V3 genotypic tropism assay: a retrospective analysis using screening samples from the A4001029 and MOTIVATE studies. *AIDS*. 2010;24(16):2517-2525. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20736814.
14. McGovern RA, Thielen A, Portsmouth S, et al. Population-based sequencing of the V3-loop can predict the virological response to maraviroc in treatment-naive patients of the MERIT trial. *J Acquir Immune Defic Syndr*. 2012;61(3):279-286. Available at http://www.ncbi.nlm.nih.gov/pubmed/23095934.
15. Archer J, Weber J, Henry K, et al. Use of four next-generationsequencing platforms to determine HIV-1 coreceptor tropism. *PLoS One.* 2012;7(11):e49602. Available at http://www.ncbi.nlm.nih.gov/pubmed/23166726.
16. Vandekerckhove LP, Wensing AM, Kaiser R, et al. European guidelines on the clinical management of HIV-1 tropism testing. *Lancet Infect Dis*. 2011;11(5):394-407. Available at http://www.ncbi.nlm.nih.gov/pubmed/21429803.

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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 ABC HSR is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5%–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 patients 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 patients on an ABC-containing regimen **(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

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readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

References

1. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001;23(10):1603-1614.
2. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359(9308):727-732.
3. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002;359(9312):1121-1122.
4. Phillips EJ, Sullivan JR, Knowles SR, et al. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS*. 2002;16(16):2223-2225.
5. Phillips E, Rauch A, Nolan D, et al. Pharmacogenetics and clinical characteristics of patch test confirmed patients with abacavir hypersensitivity. *Rev Antivir Ther*. 2006:3: Abstract 57.
6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118.

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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 HIV-infected cohorts (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:

- low baseline viremia,
- high potency of the ARV regimen,
- tolerability of the regimen,
- convenience of the regimen,
- 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

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treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART. (See Adherence to Antiretroviral Therapy.)

References

1. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. Jul 15 2010;363(3):257-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20647201.
2. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. Jul 20 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.
3. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.
4. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. Apr 30 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19339714.
5. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. Aug 5 1999;341(6):385-393. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432323.
6. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009;338:b1649. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19406887.
7. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.
8. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. Feb 20 2011;25(4):473-477. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160416.
9. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med*. Feb 15 1996;334(7):426-431. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8552144.
10. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr*. Jun 1 2004;36(2):702-713. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15167289.
11. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. Nov 30 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.

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Initiation of Antiretroviral Therapy (Last updated January 28, 2016; last reviewed January 28, 2016)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection **(AI)**. • ART is also recommended for HIV-infected individuals to prevent HIV transmission **(AI)**. • When initiating ART, it is important to educate patients regarding the benefits and considerations regarding 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 HIV-infected individuals 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, and effective ART can reduce viremia and transmission of HIV to sexual partners by more than 96%.[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, HIV-infected individuals 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 HIV-infected individuals to medical care before they have advanced HIV disease. Deferring ART until CD4 counts decline puts HIV-infected individuals at risk of 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 6 years on ART[5] and have a shorter life expectancy than those initiating therapy at higher CD4 count thresholds.[5,6]

For the above reasons, since 2012, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) has recommended initiating ART in all HIV-infected individuals; however, based on published evidence available at the time, the strength of the recommendation has differed by CD4 count strata (**AI** for CD4 count <350 cells/mm^3, **AII** for CD4 count between 350 and 500 cells/mm^3, and **BIII** for CD4 count >500 cells/mm^3). However, findings from two large, randomized controlled trials that addressed the optimal time to initiate ART—START (Strategic Timing of Antiretroviral Therapy)[7] and TEMPRANO[8]—have led the Panel to increase the strength and evidence rating of this recommendation to **AI** for all patients, regardless of CD4 cell count. Both studies demonstrated about a 50% reduction in morbidity and mortality among HIV-infected individuals with CD4 counts >500 cells/mm^3 randomized to receive ART immediately versus delaying initiation of ART (described in more detail below). 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

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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 HIV-infected individuals, regardless of CD4 cell count, to reduce the morbidity and mortality associated with HIV infection **(AI)**. ART is also recommended for HIV-infected individuals 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 HIV-infected pregnant women)[9]
- 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.[10] Similarly, although an IRIS-like presentation of non-Hodgkins lymphoma after initiation of ART has been described,[11] greater ART-mediated viral suppression is also associated with longer survival among individuals undergoing treatment for AIDS lymphoma.[12] Drug interactions should be considered when selecting ART given the potential for significant interactions between chemotherapeutic agents and some ARV drugs (particularly some nucleoside reverse transcriptase inhibitor [NNRTI] and ritonavir- or cobicistat-boosted regimens). However, a diagnosed 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 therapy may increase the risk of serious IRIS, a short delay before initiating ART may be warranted.[13-16] 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;[17] therefore, therapy should not be delayed.

In patients who have active non-meningeal tuberculosis, initiating ART during treatment for tuberculosis confers a significant survival advantage;[18-22] therefore, ART should be initiated as recommended in Mycobacterium Tuberculosis Disease with HIV Coinfection.

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Clinicians should refer to the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[10] 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 patients will be diagnosed early in the course of HIV infection. Unfortunately, some patients with HIV infections are still diagnosed at later stages of 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[23] 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, injection drug users, and older adults than in other populations, and many individuals in these groups develop AIDS-defining illnesses within 1 year of diagnosis.[24-26] 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 newly diagnosed patients are educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once patients are in care, focused effort is required to retain them in the health care system so that both the infected individuals and their sexual partners can fully benefit from early diagnosis and treatment.

Evidence Supporting Benefits of ART to Prevent Morbidity and Mortality

Although observational studies had been inconsistent in defining the optimal time to initiate ART,[27-30] randomized controlled trials now definitively demonstrate that ART should be initiated in all HIV-infected patients, 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.[17,31] 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.[32] 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 HIV-infected patients 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 early 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 delayed 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, $P <$

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.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 (HR 0.61, [95% CI, 0.38–0.97, $P = 0.04$]).[7]

The TEMPRANO ANRS 12136 study was a randomized controlled trial conducted in Cote d'Ivoire. Using a two-by-two factorial design, HIV-infected participants with 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.[8]

The TEMPRANO and START trials had very similar estimates of the protective effect of immediate ART among HIV-infected individuals with 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 ART 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.[33-38] 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.[39-41] 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 ART 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 the HIV-infected individual 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.[42,43] 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.[1,44]

Most significantly, the multi-continental HPTN 052 trial enrolled 1,763 HIV-serodiscordant couples in which the HIV-infected partner 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 HIV-uninfected partner.[2] At study entry, 97% of the participants reported to be in a

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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 1 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 HIV-infected partner was taking ART as prescribed and viral load was suppressed.[45] Notably, there were only eight cases of HIV transmission within couples after the HIV-infected partner started ART; four transmissions occurred before the HIV-infected partner 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, demonstrates that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted diseases (STDs) 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 STDs (see Preventing Secondary Transmission of HIV).

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 HIV-infected pregnant women, 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 ART

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[7] and TEMPRANO[8] 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. ART initiation may need to be briefly delayed to resolve issues identified during such discussions.

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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 Antiretroviral Therapy. 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 section).

Considerations for Special Populations

Elite HIV Controllers

A small subset of HIV-infected individuals maintains plasma HIV-1 RNA levels below level of quantification for years without ART. These individuals are often referred to as "elite HIV controllers."[53,54] 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.[53,55-57] 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.[58] Moreover, elite controllers with preserved CD4 counts appear to experience a decline in immune activation after ART initiation, suggesting that treatment may be beneficial.[59] 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.

HIV-Infected Adolescents

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.[60] 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 HIV-Infected Adolescents section).[61]

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Conclusion

The results of definitive randomized controlled trials support the Panel's recommendation to initiate ART to all HIV-infected individuals, 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 HIV-infected patients 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.

References

1. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. Mar 30 2000;342(13):921-929. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10738050.
2. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.
3. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. Jan 3 2009;373(9657):48-57. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19038438.
4. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. *Clin Infect Dis*. Jun 1 2010;50(11):1512-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/20415573.
5. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. Feb 1 2007;44(3):441-446. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205456.
6. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8(12):e81355. Available at http://www.ncbi.nlm.nih.gov/pubmed/24367482.
7. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. Jul 20 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.
8. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.
9. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed January 12, 2016.
10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 12, 2016.
11. Gopal S, Patel MR, Achenbach CJ, et al. Lymphoma immune reconstitution inflammatory syndrome in the center for AIDS research network of integrated clinical systems cohort. *Clin Infect Dis*. Jul 15 2014;59(2):279-286. Available at http://www.ncbi.nlm.nih.gov/pubmed/24755860.
12. Gopal S, Patel MR, Yanik EL, et al. Association of early HIV viremia with mortality after HIV-associated lymphoma. *AIDS*. Sep 24 2013;27(15):2365-2373. Available at http://www.ncbi.nlm.nih.gov/pubmed/23736149.
13. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. Jun 2011;52(11):1374-1383. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21596680.
14. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N*

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Engl J Med. Jun 26 2014;370(26):2487-2498. Available at http://www.ncbi.nlm.nih.gov/pubmed/24963568.

15. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. Nov 15 2005;41(10):1483-1497. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16231262.
16. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr*. Jun 1 2009;51(2):130-134. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19365271.
17. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19440326.
18. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *J Acquir Immune Defic Syndr*. Feb 1 2009;50(2):148-152. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19131895.
19. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20181971.
20. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. Oct 20 2011;365(16):1492-1501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010915.
21. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1471-1481. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010913.
22. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1482-1491. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010914.
23. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16988643.
24. Wolbers M, Bucher HC, Furrer H, et al. Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med*. Jul 2008;9(6):397-405. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18410354.
25. Centers for Disease Control and Prevention. Late HIV testing—34 states, 1996–2005. *MMWR Morb Mortal Wkly Rep*. Jun 26 2009;58(24):661-665. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19553901.
26. Grigoryan A, Hall HI, Durant T, Wei X. Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996–2004. *PLoS One*. 2009;4(2):e4445. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19214229.
27. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. Apr 30 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19339714.
28. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. Apr 18 2009;373(9672):1352-1363. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19361855.
29. CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med*. Sep 26 2011;171(17):1560-1569. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21949165.
30. Cain LE, Logan R, Robins JM, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med*. Apr 19 2011;154(8):509-515. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21502648.
31. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

Trials Group 320 Study Team. *N Engl J Med*. Sep 11 1997;337(11):725-733. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9287227.

32. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. Jul 15 2010;363(3):257-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20647201.
33. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. Jan 17 2013;368(3):218-230. Available at http://www.ncbi.nlm.nih.gov/pubmed/23323898.
34. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. May 15 2003;187(10):1534-1543. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12721933.
35. Mocroft A, Phillips AN, Gatell J, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet*. Aug 4 2007;370(9585):407-413. Available at http://www.ncbi.nlm.nih.gov/pubmed/17659333.
36. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. Mar 15 2009;48(6):787-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/19193107.
37. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS*. Sep 26 2003;17(14):2015-2023. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14502004.
38. Robbins GK, Spritzler JG, Chan ES, et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. *Clin Infect Dis*. Feb 1 2009;48(3):350-361. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19123865.
39. Jain V, Hartogensis W, Bacchetti P, et al. Antiretroviral therapy initiated within 6 months of HIV infection is associated with lower T-cell activation and smaller HIV reservoir size. *J Infect Dis*. Oct 15 2013;208(8):1202-1211. Available at http://www.ncbi.nlm.nih.gov/pubmed/23852127.
40. Burdo TH, Lentz MR, Autissier P, et al. Soluble CD163 made by monocyte/macrophages is a novel marker of HIV activity in early and chronic infection prior to and after anti-retroviral therapy. *J Infect Dis*. Jul 1 2011;204(1):154-163. Available at http://www.ncbi.nlm.nih.gov/pubmed/21628670.
41. Okulicz JF, Le TD, Agan BK, et al. Influence of the timing of antiretroviral therapy on the potential for normalization of immune status in human immunodeficiency virus 1-infected individuals. *JAMA Intern Med*. Jan 2015;175(1):88-99. Available at http://www.ncbi.nlm.nih.gov/pubmed/25419650.
42. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS*. Jan 28 2000;14(2):117-121. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10708281.
43. Coombs RW, Reichelderfer PS, Landay AL. Recent observations on HIV type-1 infection in the genital tract of men and women. *AIDS*. Mar 7 2003;17(4):455-480. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12598766.
44. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. Mar 1 2002;29(3):275-283. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11873077.
45. Cohen M, HPTN 052 Study Team. Antiretroviral treatment prevents HIV transmission: final results from the HPTN 052 randomized controlled trial. Presented at: 8th IAS Conference on HIV Pathogenesis, Treatment, and Prevention. 2015. Vancouver, Canada.
46. Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr*. Sep 1 2005;40(1):96-101. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16123689.
47. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*. Jan 2 2006;20(1):85-92. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327323.
48. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a

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model-based analysis. *Lancet*. Jul 26 2008;372(9635):314-320. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18657710.

49. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. Feb 20 2011;25(4):473-477. Available at http://www.ncbi.nlm.nih.gov/pubmed/21160416.
50. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. Feb 15 2010;50(4):585-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/20070234.
51. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. May 11 2008;22(8):973-981. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18453857.
52. Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr*. Aug 1 2009;51(4):450-453. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19474757.
53. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis*. Jan 1 2008;197(1):126-133. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171295.
54. Choudhary SK, Vrisekoop N, Jansen CA, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol*. Aug 2007;81(16):8838-8842. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17537849.
55. Pereyra F, Lo J, Triant VA, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. *AIDS*. Nov 28 2012;26(18):2409-2412. Available at http://www.ncbi.nlm.nih.gov/pubmed/23032411.
56. Hsue PY, Hunt PW, Schnell A, et al. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS*. Jun 1 2009;23(9):1059-1067. Available at http://www.ncbi.nlm.nih.gov/pubmed/19390417.
57. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis*. Mar 2014;209(6):931-939. Available at http://www.ncbi.nlm.nih.gov/pubmed/24185941.
58. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. *J Infect Dis*. Jun 1 2015;211(11):1692-1702. Available at http://www.ncbi.nlm.nih.gov/pubmed/25512624.
59. Hatano H, Yukl SA, Ferre AL, et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. *PLoS Pathog*. 2013;9(10):e1003691. Available at http://www.ncbi.nlm.nih.gov/pubmed/24130489.
60. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr*. Oct 1 2011;58(2):193-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/21826014.
61. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. Mar 2009;23(3):185-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/19866536.

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What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) 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 (booster) (cobicistat or ritonavir).
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as Recommended regimens for antiretroviral therapy (ART)-naive patients:

  Integrase Strand Transfer Inhibitor-Based Regimens:
  - Dolutegravir/abacavir/lamivudine[a]—**only** for patients who are HLA-B*5701 negative **(AI)**
  - Dolutegravir plus either tenofovir disoproxil fumarate/emtricitabine[a] **(AI)** or tenofovir alafenamide/emtricitabine **(AII)**
  - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine **(AI)**
  - Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine **(AI)**
  - Raltegravir plus either tenofovir disoproxil fumarate/emtricitabine[a] **(AI)** or tenofovir alafenamide/emtricitabine **(AII)**

  Protease Inhibitor-Based Regimens:
  - Darunavir/ritonavir plus either tenofovir disoproxil fumarate/emtricitabine[a] **(AI)** or tenofovir alafenamide/emtricitabine **(AII)**
- On the basis of individual patient characteristics and needs, an Alternative regimen or, less frequently, an Other regimen, may be the optimal regimen for a particular patient. A list of Alternative and Other regimens can be found in Table 6.
- 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 testing results, comorbid conditions, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 8 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.

Introduction

More than 25 antiretroviral (ARV) drugs in 6 mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). In addition, two drugs, ritonavir (RTV or r) and cobicistat (COBI or c) are used solely as pharmacokinetic (PK) enhancers (ie, boosters) to improve the PK profiles of some ARV drugs (eg, 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), tenofovir alafenamide/emtricitabine (TAF/FTC), or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), plus a drug from one of three drug classes: an INSTI, an NNRTI, or a PK-enhanced 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 HIV RNA decreases and CD4 T lymphocyte (CD4) cell increases in most patients.[1-3]

Supporting Evidence and Rationale Used for Panel's Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations are primarily

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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 views that the strongest evidence on which to base recommendations is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen has shown high rates of viral suppression, increased CD4 cell count, and has a favorable safety profile. 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 from trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. In this section of the guidelines, the definition of 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, ease of use, 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 Recommended, Alternative, or Other regimens, as specified in Table 6. **Recommended regimens** are primarily those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use, including some newer combinations whose use is supported by evidence from bioequivalence/bioavailability studies or randomized switch trials. **Alternative regimens** are those that are effective but have potential disadvantages, limitations for use in certain patient populations, or less supporting data than Recommended regimens. In certain situations, depending on an individual patient's characteristics and needs, an Alternative regimen may actually be the optimal regimen for a specific patient. Some regimens are classified as **Other regimens** because, when compared with Recommended or Alternative regimens, they have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations.

In addition to Table 6, a number of tables presented below and at the end of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Adult and Adolescent Guidelines) provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 7 lists specific case scenarios to guide regimen selection for patients with common clinical conditions. Table 8 lists the potential advantages and disadvantages of the components used in Recommended and Alternative regimens. Table 9 lists agents or regimens not recommended for initial treatment. Appendix B, Tables 1–6 lists characteristics of individual ARV agents (eg, formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 7 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, new data from clinical trials and cohort studies, as well as experience in clinical practice, have prompted several changes to the list of Recommended, Alternative, and Other regimens for treatment-naive patients (Table 6). Among these changes, the following deserve emphasis:

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- TAF, an oral prodrug of tenofovir (TFV), is now included as a component of several Recommended regimens, including EVG/c/TAF/FTC, dolutegravir (DTG) plus TAF/FTC, darunavir/ritonavir (DRV/r) plus TAF/FTC, and raltegravir (RAL) plus TAF/FTC. These recommendations are based on data from comparative trials demonstrating that TAF-containing regimens are as effective in achieving[4] or maintaining virologic suppression[5] as TDF-containing regimens but with more favorable effects on markers of renal and bone health. In these studies, participants randomized to receive TDF had more favorable lipid profiles than those who received TAF.[4,5] Unlike TDF, which should be avoided or dose-reduced in patients with estimated creatinine clearance (CrCl) <50 to 60 mL/min, TAF-containing regimens appear to be safe and are FDA approved for use in patients with estimated CrCl as low as 30 mL/min.
- The list of Alternative regimens has also been expanded to include TAF/FTC in combination with EFV, rilpirivine (RPV), COBI- or RTV-boosted atazanavir (ATV/c or ATV/r), or COBI-boosted DRV (DRV/c).
- Guidance for clinicians on choosing between ABC-, TAF-, and TDF-containing regimens has been added to the Adult and Adolescent Guidelines.
- Lopinavir/ritonavir (LPV/r) plus 2-NRTI regimen has been removed from the list of Other regimens because therapies containing this PI combination have a larger pill burden and greater toxicity than other currently available options.

Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, and resistance test results. Some regimens listed in this table may not be appropriate for patients with renal impairment. See Appendix B, Table 7, and the product prescribing information for recommendations on ARV dose modification in the setting of renal impairment. Drug classes and regimens within each class are arranged first by evidence rating and when ratings are equal, in alphabetical order.

Recommended Regimen Options Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2-NRTI Regimen: • DTG/ABC/3TC[a] **(AI)—if HLA-B*5701 negative** • DTG plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)** • EVG/c/TAF/FTC **(AI)** or EVG/c/TDF/FTC **(AI)** • RAL plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)** Boosted PI plus 2 NRTIs: • DRV/r plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**
Alternative Regimen Options Alternative regimens are effective and tolerable, but have potential disadvantages when compared with the Recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **However, an Alternative regimen may be the preferred regimen for some patients.**
NNRTI plus 2 NRTIs: • EFV/TDF/FTC[a] **(BI)** • EFV plus TAF/FTC[b] **(BII)** • RPV/TDF/FTC[a] **(BI)** or RPV/TAF/FTC[b] **(BII)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** Boosted PI plus 2 NRTIs: • (ATV/c or ATV/r) plus either TDF/FTC[a] **(BI)** or TAF/FTC[b] **(BII)** • DRV/c **(BIII)** or DRV/r **(BII)** plus ABC/3TC[a]—if HLA-B*5701 negative • DRV/c plus either TDF/FTC[a] **(BII)** or TAF/FTC[b] **(BII)**

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Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients (page 2 of 2)

Other Regimen Options
When compared with Recommended and Alternative regimens, Other regimens may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations.
If HIV RNA <100,000 copies/mL and HLA-B*5701 Negative: • ATV/c **(CIII)** or ATV/r **(CI)** plus ABC/3TC • EFV plus ABC/3TC[a] **(CI)** • RAL plus ABC/3TC[a] **(CII)** Other Regimens to Consider when TAF, TDF, or ABC Cannot be Used: • DRV/r plus RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3** • LPV/r plus 3TC[a] (BID) **(CI)**

[a] 3TC may be substituted for FTC, or vice versa, if a non-fixed dose NRTI combination is desired.

[b] The evidence supporting this regimen is based on relative bioavailability data coupled with data from randomized, controlled switch trials demonstrating the safety and efficacy of TAF-containing regimens.

Note: The following are available as coformulated products: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, and TDF/FTC.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

Initial therapy generally consists of 2 NRTIs combined with an INSTI, an NNRTI, or a PK-enhanced PI.

Choosing the 2 NRTIs

All Recommended and Alternative regimens include an NRTI combination of ABC/3TC, TAF/FTC, or TDF/FTC, each of which is available as a fixed-dose combination tablet. The choice of NRTI combination is usually guided by differences between ABC, TAF, and TDF, because FTC and 3TC have few adverse events and comparable efficacy. The main advantages of TAF and TDF over ABC are their activity against hepatitis B virus (HBV) (relevant in HBV-coinfected patients) and the fact that HLA-B*5701 testing is not required their use. Moreover, TDF has been associated with favorable lipid effects. However, TDF use has been associated with declines in kidney function, proximal renal tubulopathy (leading to proteinuria and phosphate wasting), and reductions in bone mineral density (BMD). These tenofovir toxicities are less common with TAF, which results in lower plasma tenofovir concentrations than TDF. As a result, the main advantages of TAF over TDF are TAF's more favorable effects on renal markers and BMD.[5-7] TAF has less favorable lipid effects than TDF, probably because of lower tenofovir plasma concentrations. The main advantages of ABC over TDF are that it does not require dose adjustment in patients with renal insufficiency and has less nephrotoxicity and less deleterious effects on BMD than TDF. However, ABC use has been linked to cardiovascular events in some, but not all, observational studies. There have been no head-to-head studies comparing ABC and TAF. Considerations germane to the choice between TAF, TDF, and ABC in specific clinical scenarios are summarized in Table 7, Table 8, and in the section on dual NRTI options below.

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

The choice between an INSTI, NNRTI, or PI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, genetic barrier to resistance, adverse effects profile, and convenience. The patient's co-

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morbidities, concomitant medications, and the potential for drug-drug interactions should also be considered (see Tables 7 and 8 for guidance). The Panel's Recommended regimens as listed in Table 6 include an INSTI or DRV/r in combination with 2 NRTIs. For most patients, an INSTI-containing regimen will be highly effective, have few adverse effects, and (with RAL and DTG) have no significant CYP 3A4-associated drug interactions. In addition, in several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI was better tolerated with fewer treatment discontinuations.[8-10] For these reasons, all three currently available INSTIs are included among the Recommended regimens and, in general, should be selected for most patients. An exception is in those individuals with uncertain adherence or in whom treatment needs to begin before resistance testing results are available (eg, during acute HIV infection, pregnancy, in the setting of certain opportunistic infections). In this context, DRV/r may have an important role given the low rate of transmitted PI resistance, its high genetic barrier to resistance, and low rate of treatment-emergent resistance during many years of clinical experience. DTG may also be considered for patients who must start ART before resistance testing results are available. Because of its high barrier to resistance, DTG resistance is uncommon in those failing therapy and transmitted resistance has not yet been identified.

Alternative Regimens include either an NNRTI-based (EFV or RPV) or a PK-enhanced, PI-based (ATV/r, ATV/c, or DRV/c) regimen. Although the NNRTIs EFV or RPV are optimal choices for some patients, these drugs have low genetic barriers to resistance, especially in patients with suboptimal adherence. EFV has a long track record of widespread use in the United States and globally. Most EFV-based regimens have strong 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 makes the EFV-based regimen less tolerable than other regimens. RPV has fewer adverse effects than EFV, is available as one of the smallest coformulated single tablets, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA (>100,000 copies/mL) and low CD4 count (<200 cells/mm^3). ATV/r has demonstrated excellent virologic efficacy in clinical trials and has relatively few metabolic adverse effects in comparison to other boosted PI regimens; however, clinical trial data showed that ATV/r had a higher rate of adverse effect-associated drug discontinuation than DRV/r and RAL.[8] Thus, despite these favorable attributes, based on the above considerations, EFV-, RPV-, and ATV/r-containing regimens are now listed as Alternative regimens for initial therapy. However, based on individual patient characteristics, some Alternative regimens may actually be the optimal regimen for some patients. Furthermore, patients who are doing well on EFV-, RPV-, and ATV/r-containing regimens should not necessarily be switched to other agents.

Factors to Consider When Selecting an Initial Regimen

When selecting a regimen for an individual patient, 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 can be grouped into the following categories:

Initial Characteristics to Consider in All Patients:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 cell count
- HIV genotypic drug resistance testing 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
- Patient preferences
- Anticipated adherence to the regimen

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Specific Comorbidities or Other Conditions:

- Cardiovascular disease, hyperlipidemia, renal disease, osteopenia/osteoporosis or conditions associated with BMD loss, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or pregnancy potential. Clinicians should refer to the latest Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States (Perinatal Guidelines) for more detailed recommendations on the safety and effectiveness of ARV drugs during pregnancy.
- Coinfections: hepatitis B (HBV), hepatitis C (HCV), tuberculosis (TB)

Regimen-Specific Considerations:

- Regimen's genetic barrier to resistance
- Potential adverse drug effects
- Known or potential drug interactions with other medications
- Convenience (eg, pill burden, dosing frequency, availability of fixed-dose combination products, food requirements)
- Cost (see Cost Consideration and Antiretroviral Therapy)

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

This table is designed to guide 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 patient, 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 patient 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 8 for additional information regarding the advantages and disadvantages of particular ARV medications.

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/ mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	Higher rate of virologic failure observed in those with low pretreatment CD4 cell count.
	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 observed in those with high pretreatment HIV RNA.
	HLA-B*5701 positive	**Do not use ABC-containing regimen.**	Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.
	Must treat before HIV drug resistance results available	**Avoid NNRTI-based regimens.** Recommended ART Regimens: • DRV/r plus TAF/FTC or TDF/FTC • DTG plus TAF/FTC or TDF/FTC	Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. Resistance to DRV/r and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics	One pill once daily regimen is desired	ART Options Include: • DTG/ABC/3TC • EFV/TDF/FTC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use RPV-based regimens if HIV RNA >100,000 copies/mL and CD4 count <200/mm^3 Do not use a regimen including ABC if HLA-B*5701 positive See Appendix B, Table 7 for recommendations on ARV dose modification in the setting of renal impairment.
	Food effects	Regimens that Can be Taken Without Regard to Food: • RAL- or DTG-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens that Should be Taken with Food: • ATV/r or ATV/c-based regimens • DRV/r or DRV/c-based regimens • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV-based regimens	Food improves absorption of these listed 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 eGFR <60 mL/min)	**Avoid TDF.** Use ABC or TAF. ABC may be used if 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 eGFR >30 mL/min Other Options When ABC or TAF Cannot be Used (See Text for Discussion): • LPV/r plus 3TC; *or* • RAL plus DRV/r (if CD4 count >200 cells/mm^3, HIV RNA <100,000 copies/mL)	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction reported in patients using TDF in conjunction with RTV-containing regimens. TAF has less impact on renal function and lower rates of proteinuria than TDF. ABC has not been associated with renal dysfunction. See Appendix B, Table 7 for recommendations on ARV dose modification in patients with renal insufficiency.
	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 7 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 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 bone mineral density along with renal tubulopathy, urine phosphate wasting and resultant osteomalacia. TAF and ABC are associated with smaller declines in bone mineral density than TDF.

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

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.**	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality.
	HIV-associated dementia (HAD)	**Avoid EFV-based regimens if possible.** Favor DRV-based or DTG-based regimens.	EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms. Theoretical CNS penetration advantage
	Narcotic replacement therapy required	**If patient is receiving methadone, consider avoiding EFV-based regimens.** If EFV is used, an increase in methadone dose may be necessary.	EFV reduces methadone concentrations and may lead to withdrawal symptoms.
	High cardiac risk	**Consider avoiding ABC- and LPV/r -based regimens.**	Increased cardiovascular risk in some studies
	Hyperlipidemia	The Following ARV Drugs have been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c	DTG and RAL have fewer lipid effects. TDF has been associated with more favorable lipid effects than ABC or TAF.
	Pregnancy	Refer to the Perinatal Guidelines.	
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 active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection.	
	Treating TB disease with rifamycins	TAF is not recommended with any rifamycin-containing regimen. If Rifampin is Used: • EFV can be used without dosage adjustment • If RAL is used, increase RAL dose to 800 mg BID. • Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label). If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.	• Rifamycins may significantly reduce TAF exposure. • Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PI, INSTI, and RPV. • Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs. • Rifabutin is a less potent inducer and is a good option for patients receiving non-EFV-based regimens. Refer to Tables 19a, b, d and e for dosing recommendations for rifamycins used with different ARV agents.

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ARV = antiretroviral; c = cobicistat; CKD = chronic kidney disease; CrCl = creatinine clearance; DRV/r = darunavir/ritonavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Choosing Among Different Drugs from an Antiretroviral Drug Class

The sections below provide clinicians with comparisons of different, currently recommended ARV drugs within a drug class. These comparisons include information related to the safety and virologic efficacy of different drugs based on clinical trial results and/or post-marketing data, specific factors to consider, and the rationales for the Panel's recommendations.

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

Summary

ABC/3TC, TAF/FTC, and TDF/FTC are NRTI combinations recommended for use as components of initial therapy. Table 6 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.

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, either with the same[11-13] or a different (third) ARV drug (also see discussion in the Dolutegravir section).[14]

- The ACTG 5202 study, a randomized controlled trial in more than 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.
  - Treatment randomization was stratified on the basis of a screening HIV RNA level <100,000 copies/mL or ≥100,000 copies/mL. HLA-B*5701 testing was not required before study entry.
  - A Data Safety Monitoring Board recommended early termination of the ≥100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the ABC/3TC arm than in the TDF/FTC arm.[11] This difference in time to virologic failure between the arms was observed regardless of whether the third active drug was EFV or ATV/r.
  - There was no difference in time to virologic failure between ABC/3TC and TDF/FTC for participants who had plasma HIV RNA <100,000 copies/mL at screening.[15]
- 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.[12]
- 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. In a subgroup analysis of patients with baseline HIV RNA ≥100,000 copies/mL, the proportion of participants who achieved HIV RNA <50 copies/mL at 96 weeks did not differ between the two regimens.[13]

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To date, there are no published results from a head-to-head clinical trial comparing ABC and TAF.

Tenofovir Alafenamide Compared with 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 1,584 ART-naive adults with estimated glomerular filtration rate (eGFR) ≥50 mL/min.
  - At 48 weeks, 92% of participants randomized to receive TAF and 90% of those randomized to receive TDF achieved plasma HIV RNA <50 copies/mL, demonstrating that TAF was noninferior to TDF when combined with EVG/c/FTC. Both regimens were well tolerated. The studies did not have adequate power to assess whether renal failure and fracture rates were different between the TAF and TDF groups.[6]
  - Participants in the TAF arm had significantly smaller reductions in BMD at the spine and the hip than those in the TDF arm.
  - Through 96 weeks, change from baseline eGFR and renal biomarkers favored EVG/c/TAF/FTC, and renal tubular function was less affected by the EVG/c/TAF/FTC regimen than by the EVG/c/TDF/FTC regimen. Clinically significant renal events, including discontinuations for renal adverse events, were less frequent in participants receiving EVG/c/TAF/FTC than in those treated with EVG/c/TDF/FTC.[16] A subset analysis of patients at high risk for chronic kidney disease showed a lower rate of at least 25% decline in eGFR in patients on EVG/c/TAF/FTC, compared to patients on EVG/c/TDF/FTC (11.5% vs. 24.9%, $P < 0.001$).[7]
  - Fasting lipid levels, including 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.[4]
- Combination TAF/FTC was also approved based on efficacy and safety data from one switch study in virologically suppressed patients.[5] This study included 663 patients with HIV-1 RNA <50 copies/mL for at least 6 months on a regimen containing TDF/FTC. Participants were randomized to continue TDF/FTC or switch to TAF/FTC.
  - At 48 weeks, TAF/FTC was noninferior to TDF/FTC in that viral suppression was maintained by 94.3% and 93% of the particpants, respectively.
  - Improvement in eGFR and renal biomarkers was more frequent in those switched to TAF/FTC. BMD improved in those switched to TAF/FTC but declined in those continuing on TDF/FTC.
  - Fasting lipid levels increased more in those who switched to TAF/FTC than in those who continued TDF/FTC.
- To assess the ability of TAF to maintain HIV and HBV suppression, 72 HIV/HBV coinfected patients with HIV-1 RNA <50 copies/mL and HBV DNA <9 $\log_{10}$ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[17] In this study, 96% of participants were on a TDF/FTC-containing regimen prior to the switch.
  - 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.[17]

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Dual-NRTI Choices

Note: 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.[14,18-20]

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.[21,22] HLA-B*5701 testing should precede use of ABC. ABC should not be given to patients who test positive for HLA-B*5701 and, based on a positive test result, ABC hypersensitivity should be noted on a patient's allergy list. Patients who are HLA-B*5701-negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR should never be rechallenged, regardless of their HLA-B*5701 status.

Cardiovascular Risk:

- An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational, observational study group found that recent (ie, 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.[23,24]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[25-28] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[29-33]
- 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 single-tablet regimen with DTG.
- ABC and 3TC are available separately in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or who are at high risk for renal effects. No dosage 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 ABC/3TC as a component of coformulated products, the Panel classifies DTG/ABC/3TC as a Recommended regimen **(AI)** (see 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, or RAL is only recommended for patients with pretreatment HIV RNA <100,000 copies/mL. See Table 6 for more detailed recommendations on use of ABC/3TC with these drugs.

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- 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 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:

- The potential for adverse kidney and bone effects is less likely with TAF than with TDF. In randomized controlled trials that compared TAF and TDF in treatment-naive or virally suppressed patients, TAF had more favorable effects on renal biomarkers and bone density than TDF.
- In the randomized controlled trials in ART-naive patients, as well as in switch studies, 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.

Other Factors and Considerations:

- TAF/FTC is available in fixed-dose drug combinations with EVG/c or RPV, allowing the regimens to be administered as a single pill taken once daily with food.
- TAF-containing compounds 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 (see Laboratory Testing for Initial Assessment and Monitoring of HIV-Infected Patients on Antiretroviral Therapy).
- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair of the ART regimen because the drugs have activity against both viruses (see HBV/HIV Coinfection).[17]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[34] and the combination's availability as a component of coformulated products, the Panel considers TAF/FTC a Recommended NRTI combination for initial ART in treatment-naive patients when combined with DTG **(AII)**, EVG/c **(AI)**, RAL **(AII)**, or DRV/r **(AII)**.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

TDF, with either 3TC or FTC, has been studied in combination with EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.[35-44]

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[45,46] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)[47] and pre-existing renal impairment.[48] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested a greater risk of renal dysfunction when TDF is used in these regimens.[46,49-53]

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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 comparing TDF/FTC with ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[54,55] 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.[56]

Other Factors and Considerations:

- TDF/FTC is available in fixed-dose drug combinations with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill, taken once daily.
- 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 of HIV-Infected Patients on Antiretroviral Therapy). In patients who have pre-existing renal insufficiency (CrCl <60 mL/min),[57] use of TDF should generally be avoided. If TDF is used, dosage adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 7 for dosage recommendations).
- Both TDF and FTC are active against HBV. In patients with HIV/HBV coinfection, TDF/FTC may be used as the NRTI pair of the ART regimen because the drugs have activity against both viruses (also see HBV/HIV Coinfection section).

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 coformulated products, the Panel considers TDF/FTC a Recommended NRTI combination for initial ART in treatment-naive patients when combined with DTG, EVG/c, RAL, or DRV/r. See Table 6 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.

INSTI-Based Regimens

Summary

Three INSTIs—DTG, EVG, and RAL—are currently approved for HIV-infected, ARV-naive patients. DTG and EVG are currently available as components of one-tablet, once daily complete regimens: DTG is coformulated with ABC/3TC; EVG is coformulated with a PK enhancer (COBI) and TAF/FTC or TDF/FTC. 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.

Recommended Integrase Strand Transfer Inhibitor-Based Regimens

Note: In alphabetical order

Dolutegravir (DTG)

DTG is an INSTI with a higher genetic barrier to resistance than EVG or RAL. In treatment-naive patients, DTG is given once daily, with or without food.

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Efficacy in Clinical Trials:

The efficacy of DTG in treatment-naive patients has been evaluated in 3, fully powered clinical trials, including two randomized double-blinded clinical trials and one randomized open-label clinical trial. In these three 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.

- 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 2-NRTI regimen, either ABC/3TC or TDF/FTC, to 822 participants. At week 96, DTG was noninferior to RAL.[44]
- The SINGLE trial compared 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.[14] At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[58]
- 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 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.[59,60] The difference in response rates favoring DTG was greater in patients with pretreatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.[61]

Adverse Effects:

- DTG is generally well tolerated. The most common adverse reactions of moderate to severe intensity with an incidence ≥2% in the clinical trials were insomnia and headache. Cases of HSRs were reported in <1% of trial participants.

Other Factors and Considerations:

- DTG 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 few drug interactions. DTG increases metformin levels approximately 2-fold; close monitoring for metformin adverse effects is advisable. Rifampin decreases DTG levels; therefore, an increase in dosing of DTG to 50 mg twice daily is required.
- DTG absorption may be reduced when the ARV is coadministered with polyvalent cations (see 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 for initial therapy, which suggests that DTG has a higher genetic barrier to resistance than other INSTIs.

The Panel's Recommendation:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI)**, TAF/FTC **(AII)**, or TDF/FTC **(AI)** as a Recommended regimen in ART-naive patients.

Elvitegravir (EVG)

EVG is available as a component of 2 fixed-dose combination products containing EVG, COBI, TDF, and FTC or EVG, COBI, TAF, and FTC. COBI is a specific, potent CYP3A inhibitor that has no activity against

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HIV. It acts as a PK enhancer of EVG, which allows for once daily dosing of the combination.

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ARV-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.[62]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[63]
  - In a randomized, blinded trial performed in HIV-infected women, 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.[10]
- The efficacy of EVG/c/TAF/FTC in ARV-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR ≥50mL/min.[4,6]
  - At 48 and 96 weeks, TAF was noninferior to TDF when both were combined with EVG/c/FTC (see details in NRTI discussion).

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[62,63]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[64]

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 Interactions).[65]
- EVG plasma concentrations are lower when it is administered simultaneously with polyvalent cation-containing antacids or supplements (see Drug Interactions section). 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.[66] Patients with a confirmed increase in serum creatinine greater than 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.[53]
- EVG/c/TDF/FTC **is not recommended** for patients with pre-treatment estimated CrCl <70 mL/min.[53]
- EVG/c/TAF/FTC **is not recommended** for patients with pre-treatment 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.[62,63] These mutations conferred cross-resistance to RAL, with most retaining susceptibility to DTG.

The Panel's Recommendation:

- On the basis of the above factors, the Panel classifies EVG/c/TAF/FTC as a Recommended initial regimen for patients with estimated CrCl ≥30 mL/min **(AI)** and EVG/c/TDF/FTC for patients with estimated CrCl ≥70 mL/min **(AI)**.

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Raltegravir (RAL)

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

Efficacy in Clinical Trials:

- The efficacy of RAL (with either TDF/FTC or ABC/3TC) as initial therapy has been evaluated in two randomized, double-blinded, controlled clinical trials, and a third open-label, randomized trial.
  - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[40] RAL was superior to EFV at 4 and 5 years,[43,67] 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 in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.
  - The SPRING-2 trial also provided non-randomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 and 125 participants with baseline viral loads ≥100,000 copies/mL and <100,000 copies/mL, respectively) 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.[44]
  - ACTG A5257, a large randomized open-label trial, compared 3 NNRTI-sparing regimens containing RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all 3 regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the ritonavir-boosted protease inhibitor (PI/r) arms than in the RAL arm, and bone mineral density decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[8]

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 hypersensitivity reactions in patients who received RAL have been reported during post-marketing surveillance.[68]

Other Factors and Considerations:

- RAL must be administered twice daily—a potential disadvantage when comparing RAL-based treatment with other Recommended regimens.
- Coadministration of RAL with aluminum- and/or magnesium-containing antacids can reduce absorption of RAL and is not recommended. RAL may be coadministered with calcium carbonate-containing antacids. Polyvalent cation-containing supplements may also reduce absorption of RAL; thus, RAL should be given at least 2 hours before or 6 hours after cation-containing supplements.
- RAL has a lower genetic barrier to resistance than RTV-boosted PIs and DTG.

The Panel's Recommendations:

- On the basis of these data and long-term clinical experience with RAL, the Panel considers RAL plus TDF/FTC **(AI)** or TAF/FTC **(AII)** as a Recommended regimen in ARV-naive patients.
- Because few 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 an Other regimen option **(BII)**.

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Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Summary

Five NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], nevirapine [NVP], and RPV) are currently FDA-approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs are the prevalence of NNRTI-resistant viral strains in ART-naive patients[69] and the drugs' low genetic 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) may occur with a single mutation; within-class cross-resistance is common. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross resistance to other NNRTIs, including ETR.[70,71] EFV- and RPV-based regimens are now categorized as Alternative regimens as initial therapy for ART-naive patients for the following reasons:

1. Their low genetic barrier for resistance;
2. EFV is less well tolerated than the Recommended regimens; and
3. In a randomized controlled trial that compared RPV and EFV, the rate of virologic failure among participants with high pre-treatment viral load (>100,000 copies/mL) or low CD4 cell count (<200 cells/mm^3) was higher among the RPV-treated participants.

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 in ART-naive patients have demonstrated superiority or noninferiority to several comparator regimens.

- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[72]
- 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 was more frequent with RPV failure.[73]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[62]

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.[14]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks.[40] RAL was superior to EFV at 4 and 5 years,[43,67] 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.[74]

ENCORE 1, a multinational randomized placebo-controlled trial compared 2 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.[75] Study drug-related adverse

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events were less frequent in the EFV 400 mg group than in the 600 mg group. Although there were fewer self-reported CNS events in the 400 mg group, the groups had similar rates of psychiatric events. Unlike the 600 mg dose of EFV, the 400 mg dose is not approved for initial treatment and is not coformulated in a fixed-dose combination tablet.

Adverse Effects:

- EFV can cause CNS side effects (eg, abnormal dreams, dizziness, headache, depression), which resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur. An analysis of 4 AIDS Clinical Trial Group (ACTG) comparative trials showed a higher rate of suicidality (ie, reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens.[76] This association, however, was not found in analyses of 3 large observational cohorts.[77,78]
- EFV may cause elevation in LDL cholesterol and triglycerides.

Other Factors and Considerations:

- EFV is formulated both as a single-drug tablet and in a fixed-dose combination tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6 and therefore may potentially interact with other drugs using the same pathways (see Tables 19b, 20a, and 20b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of neural tube defects have been reported after first trimester exposure in humans.[79] Alternative regimens should be considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy, before pregnancy is usually recognized, a suppressive EFV-based regimen can be continued in pregnant women who present for antenatal care in the first trimester, or may be initiated after the first trimester (see Perinatal Guidelines).

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 **(BI)** or EFV plus TAF/FTC **(BII)** as an Alternative regimen for ART-naive patients.
- Given virologic and pharmacogenetic parameters that limit its use in some patients, the Panel recommends EFV with ABC/3TC as an Other regimen, and **only** for patients with a pre-ART viral load <100,000 copies/mL and negative HLA-B*5701 status (see discussion in ABC/3TC section) **(CI)**.
- EFV at a reduced dose has not been studied in the U.S. population. The Panel cannot recommend use of reduced-dose EFV.

Rilpivirine (RPV)

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

Efficacy in Clinical Trials:

Two Phase 3 randomized, double-blinded clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with 2 NRTIs.[73] At 96 weeks, the following findings were reported:

- RPV was noninferior to EFV overall.
- Among participants with a pre-ART viral load >100,000 copies/mL, more RPV-treated than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with virologic

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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 pre-treatment CD4 counts <200 cells/mm^3 than in those with CD4 counts ≥200 cells/mm^3.

STaR, a Phase 3b, open-label study, compared the fixed-dose combinations of RPV/TDF/FTC and EFV/TDF/FTC in 786 treatment-naive patients. At 96 weeks, the following key findings were reported:[74]

- 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. In 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 fixed-dose combination tablet of RPV/TAF/FTC was approved by the FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF were similar in participants who received the single tablet formulation and in those who received the reference drugs (RPV tablet alone and TAF 10 mg/FTC coadministered with EVG/c as a fixed-dose combination), which have demonstrated safety and efficacy in clinical trials.[34]

Adverse Effects:

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer CNS adverse events (eg, abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than 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 attempted suicide. Patients with severe depressive symptoms should be evaluated to assess whether symptoms may be due to RPV and if the risks of continued treatment outweigh the benefits.

Other Factors and Considerations:

- RPV is formulated both as a single-drug tablet and in fixed-dose combination tablets with TAF/FTC and with TDF/FTC. Among available single pill regimens, 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 (at least 390 kcal).
- 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, and should be used with caution in those receiving H2 antagonists or antacids (see 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 Interactions).
- At higher than 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 Alternative regimens.
- Use of RPV with TAF/FTC **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with

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pretreatment viral load <100,000 copies/mL and CD4 count >200 cells/mm^3.

- Data on RPV with ABC/3TC are insufficient to consider recommending this regimen as a Recommended, Alternative, or Other regimen.

PI-Based Regimens

Summary

FDA-approved PIs include ATV, ATV/c, DRV, DRV/c, fosamprenavir (FPV), indinavir (IDV), LPV/r, nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV). PI-based regimens with PK enhancement have demonstrated virologic potency, durability in treatment-naive patients, and a high genetic barrier to resistance. Few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with NNRTI- and some INSTI-based regimens.[80,81] For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy due to poor adherence. All PIs (PK-enhanced by either RTV or COBI) inhibit the cytochrome (CYP) 450 3A isoenzyme, which may lead to significant drug-drug interactions (see Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of Recommended and Alternative PIs are listed in Table 8 and Appendix B, Table 3.

PIs that are recommended for use in ART-naive patients should have proven virologic efficacy, once-daily dosing, a low pill count, and good tolerability. On the basis of these criteria, the Panel considers once-daily DRV/r plus TDF/FTC as a Recommended PI regimen **(AI)**. In a large, randomized controlled trial comparing DRV/r, ATV/r, and RAL, all 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 was greater in the ATV/r arm than in the other two arms.[8] Because of the higher rate of adverse effects, the Panel now classifies regimens containing ATV/r or ATV/c as Alternative regimens **(BI)**. DRV/c-based regimens are considered Alternative PI regimens because data only exist from single-arm clinical trials and bioequivalence studies, rather than comparative clinical trials **(BII)**.

A number of 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. Two large observational cohort studies suggest that LPV/r, IDV, FPV, or FPV/r may be associated with increased rates of MI or stroke.[24,30] This association was not seen with ATV.[82] Because of the limited number of patients receiving DRV/r, this boosted-PI was not included in the analysis of the 2 studies.

LPV/r has twice the daily dose of RTV as other PI/r regimens and is associated with more metabolic complications and gastrointestinal side effects than PK-enhanced ATV or DRV. The Panel no longer recommends LPV/r plus 2-NRTI as a regimen for initial therapy, given the availability of other PIs coformulated with PK enhancers that can be given once daily and the accumulation of experience with other classes of ART regimens with fewer toxicities. LPV/r may remain an Alternative option for HIV-infected pregnant women given experience in clinical trials and clinical practice. For more detailed recommendations on ARV choices and dosing in HIV-infected pregnant women, refer to the Perinatal guidelines. LPV/r plus 3TC is an Other regimen option for patients who cannot use ABC, TAF, or TDF. Compared to other PIs, FPV/r, unboosted ATV, and SQV/r have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are not included as options for initial therapy. Nonetheless, patients who are doing well on regimens containing these PIs should not necessarily be switched to other agents.

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Recommended Protease Inhibitor-Based Regimen

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials:

- The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (800/200 mg once daily or 400/100 mg twice daily), both in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at week 48,[38] and superior at week 192.[83] 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 in combination with 2 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 load >100,000 copies/mL and secondarily due to more drug discontinuations in the DRV/r group.[9]
- 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.[8]
- A small retrospective study that followed participants for 48 weeks suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients.[84]

Adverse Effects:

- Patients starting DRV/r may develop a skin rash, which is usually mild-to-moderately severe 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.[8] The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed in participants assigned to the RAL arm than in those in the DRV/r arm at 96 weeks ($P \leq 0.02$).[85]

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 may lead to significant interactions with other medications metabolized through this same pathway (see Drug Interactions).

The Panel's Recommendation:

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with TDF/FTC **(AI)** or TAF/FTC **(AII)** as a Recommended regimen. DRV/r with ABC/3TC is considered an Alternative regimen because there are fewer studies to support its use **(BII)**.

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Alternative Protease Inhibitor-Based Regimens

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

Efficacy in Clinical Trials:

- The CASTLE study compared once-daily ATV/r (300/100 mg) with twice-daily LPV/r (400/100 mg), each in combination with TDF/FTC. In this open-label, noninferiority study, the 2 regimens showed similar virologic and CD4 responses at 96 weeks.[86]
- 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.[72] 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.[87]
- In a study comparing ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar in the two groups.[63]
- 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.[8]
- 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 pill with matching placebos.[88] Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentage of treatment discontinuing adverse events and changes in serum creatinine and indirect bilirubin levels were comparable.[89]

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.[90]
- Nephrolithiasis,[91-93] nephrotoxicity,[94] and cholelithiasis[95] have also been reported in patients who received ATV, with or without RTV.
- 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 (eg, antacids, H2 antagonists, and particularly proton pump inhibitors [PPIs]) may impair absorption of ATV. Table 19a provides recommendations for use of ATV/c or ATV/r with these agents.
- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug Interactions).

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 Alternative regimens for ART-naive patients regardless of pretreatment HIV RNA.
- The Panel recommends against the use of ATV/r or ATV/c plus ABC/3TC in patients with pre-ART HIV-1 RNA >100,000 copies/mL given inferior virologic response seen in patients with a high baseline viral

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load on ATV/r plus ABC/3TC. ATV/r or ATV/c may be used with ABC/3TC in patients whose pre-ART HIV RNA is <100,000 copies/mL **(CI)**. Because of these limitations, these regimens are classified in the Other category.

- 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.

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 each boosted drug.[96] Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that with DRV combined with RTV, bioequivalence for the C_{min} was not achieved.[97]

Efficacy in Clinical Trial:

- In a single-arm trial of treatment-naive (94%) and treatment-experienced (6%) patients, the coformulated DRV/c 800 mg/150 mg tablet was evaluated in combination with investigator-selected NRTI/NtRTI (99% of participants were given TDF/FTC). At week 48, 81% of participants achieved HIV RNA <50 copies/ml; 5% of participants discontinued treatment because of adverse events.[98]

Adverse Effects:

- In the single arm trial, the most common treatment-emergent adverse events were diarrhea, nausea, and headache.

Other Factors:

- (DRV 800 mg and COBI 150 mg) is available as a coformulated tablet.

The Panel's Recommendations:

- On the basis of the bioequivalence study and the single arm trial, the Panel recommends DRV/c plus TAF/FTC or TDF/FTC **(BII)** and DRV/c plus ABC/3TC **(BIII)** as Alternative regimens for ART-naive patients.
- 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.

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

All currently Recommended and Alternative 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 the case of a patient who is HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment.

Based on these concerns, several clinical studies have evaluated strategies using initial regimens that avoid 2 NRTIs or the NRTI drug class altogether. Many of these studies were not fully powered to permit comparisons, and regimens from these studies will not be discussed further. However, there are now sufficient data on two regimens (DRV/r plus RAL and LPV/r plus 3TC) to warrant including them as options when ABC, TAF, or TDF cannot be used.

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

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive either twice-daily RAL or once-daily TDF/FTC, both with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r

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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 count <200 cells/mm^3, however, there were more failures in the 2-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.[99] High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in 2 smaller studies of DRV/r plus RAL.[100,101]

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/uL and CD4 cell counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

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 2 NRTIs selected by the study investigators. At 48 weeks, a similar number of patients in each arm had HIV RNA <50 copies/mL, meeting the study's noninferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus 2 NRTI regimen.[102]
- Important limitations of the GARDEL study are the use of LPV/r, twice daily dosing, and the relatively high pill burden (total of 6 tablets per day). LPV/r is not considered a Recommended or Alternative initial PI because of its unfavorable adverse event and pill burden characteristics when compared to PK-enhanced ATV and DRV. Given the above limitations, the Panel recommends that LPV/r plus 3TC be considered for use only in patients who cannot take ABC, TAF, or TDF **(CI)**.

In summary, the aggregate results from these two fully powered studies with NRTI-limiting regimens demonstrate that these initial strategies have significant deficiencies when compared to standard-of-care treatment approaches. In particular, these disadvantages are related to pill burden or dosing frequency. In addition, there are concerns about the virologic efficacy of DRV/r plus RAL in patients with high viral loads or low CD4 cell counts. The Panel only recommends LPV/r plus 3TC or DRV/r plus RAL for initial therapy in situations where ABC, TAF, and TDF should be avoided. Other less well-tested NRTI-limiting combinations are not recommended at this time.

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Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 3)

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	• May cause life-threatening hypersensitivity reaction in patients 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 cardiovascular disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with EVG/c or RPV • Active against HBV • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than after initiation of TDF/FTC • Safe in patients with eGFR ≥30 mL/min	• Fasting lipid levels, including LDL and HDL cholesterol and triglycerides, increased more in the TAF group than in the TDF group. Total cholesterol to HDL ratio was unchanged.
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; recommended dual-NRTI for HIV/HBV coinfected patients • Better virologic responses than with ABC/3TC in patients with baseline viral load ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with more favorable lipid effects than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreases BMD more than other NRTI combinations
INSTI	**DTG**	• Once-daily dosing • Higher barrier to resistance than EVG or RAL • Coformulated with ABC and 3TC • No food requirement • No CYP3A4 interactions	• Oral absorption of DTG can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function • UGT substrate; potential for drug interactions (see Table 19d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
	EVG/c	• Coformulated with TDF/FTC or TAF/FTC • Once-daily dosing • 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 products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Food requirement • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)

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Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 3)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, cont'd	**RAL**	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions	• Twice-daily dosing • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported. • Oral absorption of RAL can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • UGT substrate; potential for drug interactions (see Table 19d) • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
NNRTIs	**EFV**	• Once-daily dosing • Coformulated with TDF/FTC • Long-term clinical experience • EFV-based regimens (except for EFV plus ABC/3TC) have well documented efficacy in patients with high HIV RNA.	• Transmitted resistance more common than with PIs and INSTIs • Short-and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality • Teratogenic in nonhuman primates; avoid use in women who are trying to conceive or who are sexually active and not using contraception • Dyslipidemia • Greater risk of resistance at the time of treatment failure than with PIs • Skin rash • Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a) • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities)

	RPV	• Once-daily dosing
		• Coformulated with TDF/FTC and TAF/FTC
		• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill size than other coformulated ARV drugs
		• Compared with EFV:
		  • Fewer discontinuations for CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm^3 because of higher rate of virologic failure in these patients
			• Transmitted resistance more common than with PIs and INSTIs
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimen containing EFV and two NRTIs
			• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption
			  • Contraindicated with PPIs
			  • Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information).
			• Use caution when coadministering with a drug known to increase the risk of Torsades de Pointes.
			• Depression and suicidality

PIs	**ATV/c or ATV/r**	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with PK-enhanced PIs • ATV/c and ATV/r have similar virologic activity and toxicity profiles	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice • Food requirement • Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs) • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)

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Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs, cont'd	**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 • Less long-term clinical experience than for ATV/r • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	DRV/c or DRV/r	• Once-daily dosing • Higher genetic barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure uncommon with PK-enhanced PIs	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)
	DRV/c-specific considerations	• Coformulated tablet	• Less long-term clinical experience than for DRV/r • 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 • Approval primarily based on PK data comparable to that for DRV/r rather than on trials comparing the efficacy of DRV/c and DRV/r • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.
	LPV/r	• Only RTV-coformulated PI • No food requirement • Once or twice daily dosing	• Requires 200 mg per day of RTV • 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 effect • Possible nephrotoxicity • CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; Ca = calcium; $CaCO_3$ = calcium carbonate; CD4 = CD4 T lymphocyte; CNS = central nervous system; c or COBI= cobicistat; Cr = creatinine; CrCl = creatinine clearance; CYP = cytochrome P450; DRV darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STRs = single-tablet regimens; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis

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Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Co-Formulated) 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, peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs.
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events, 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 PI/r
IDV (Unboosted)	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
IDV/r	• Fluid requirement • IDV toxicities such as nephrolithiasis, crystalluria
LPV/r plus 2 NRTI	• Higher pill burden than other PI-based regimens • Higher ritonavir dose than other PI-based regimens • GI intolerance

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Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

ARV Drugs or Components	Reasons for Not Recommending as Initial Therapy
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
CCR5 Anagonist	
MVC	• 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; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; IDV/r = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

References

1. Moore RD, Bartlett JG. Dramatic decline in the HIV-1 RNA level over calendar time in a large urban HIV practice. *Clin Infect Dis*. Sep 2011;53(6):600-604. Available at http://www.ncbi.nlm.nih.gov/pubmed/21844006.
2. Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clin Infect Dis*. Jan 1 2010;50(1):98-105. Available at http://www.ncbi.nlm.nih.gov/pubmed/19951169.
3. Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PLoS One*. 2014;9(5):e97482. Available at http://www.ncbi.nlm.nih.gov/pubmed/24830290.
4. Wohl D, Oka S, Clumeck N, et al. Brief Report: A randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: Week 96 Results. *J Acquir Immune Defic Syndr*. May 1 2016;72(1):58-64. Available at http://www.ncbi.nlm.nih.gov/pubmed/26829661.
5. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. Apr 2016;3(4):e158-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/27036991.
6. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. Jun 27 2015;385(9987):2606-2615. Available at

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

http://www.ncbi.nlm.nih.gov/pubmed/25890673.

7. Wohl D, Thalme A, Finlayson R, et al. Renal safety of tenofovir alafenamide in patients at high risk of kidney disease. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.
8. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. Oct 7 2014;161(7):461-471. Available at http://www.ncbi.nlm.nih.gov/pubmed/25285539.
9. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV*. Apr 2015;2(4):e127-136. Available at http://www.ncbi.nlm.nih.gov/pubmed/26424673.
10. Squires K, Kityo C, Hodder S, et al. Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) is superior to ritonavir (RTV) boosted Atazanavir (ATV) plus FTC/TDF in treatment naïve women with HIV-1 infection (WAVES Study). Presented at: 8th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. 2015. Vancouver.
11. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. Dec 3 2009;361(23):2230-2240. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19952143.
12. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. Sep 1 2010;55(1):49-57. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20431394.
13. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. Jul 31 2009;23(12):1547-1556. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19542866.
14. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. Nov 7 2013;369(19):1807-1818. Available at http://www.ncbi.nlm.nih.gov/pubmed/24195548.
15. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis*. Oct 2011;204(8):1191-1201. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21917892.
16. Rijnders BJ, Post FA, Rieger A, et al. Longer-term renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.
17. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfected adults. *J Acquir Immune Defic Syndr*. May 11 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/27171740.
18. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis*. Oct 1 2004;39(7):1038-1046. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15472858.
19. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr*. Jan 1 2004;35(1):22-32. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14707788.
20. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS*. Jul 23 2004;18(11):1529-1537. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15238771.
21. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. Apr 1 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18444831.
22. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. Feb 7 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18256392.
23. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. Apr 26 2008;371(9622):1417-

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

1426. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18387667.

24. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. Feb 1 2010;201(3):318-330. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20039804.
25. The SMART/INSIGHT and the D:A:D Study Groups TSIatDADSG. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. Sep 12 2008;22(14):F17-24. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753925.
26. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med*. Feb 2010;11(2):130-136. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19682101.
27. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS*. Jun 19 2011;25(10):1289-1298. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21516027.
28. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *J Acquir Immune Defic Syndr*. Jul 1 2011;57(3):245-253. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21499115.
29. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr*. May 1 2009;51(1):20-28. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19282778.
30. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. Jul 26 2010;170(14):1228-1238. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20660842.
31. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis*. Jul 1 2011;53(1):84-91. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21653308.
32. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis*. Apr 1 2011;52(7):929-940. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21427402.
33. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr*. Dec 1 2012;61(4):441-447. Available at http://www.ncbi.nlm.nih.gov/pubmed/22932321.
34. Zack J, Chuck S, Chu H, et al. Bioequivalence of the Rilpivirine/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen. *J Bioequiv Availab*. 2016;8(2):49-54. Available at http://www.omicsonline.org/open-access/bioequivalence-of-the-rilpivirineemtricitabinetenofovir-alafenamidesingletablet-regimen-jbb-1000266.pdf.
35. Cassetti I, Madruga JV, Etzel A, al. e. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients through seven years. Presented at: 17th International AIDS Conference. 2008. Mexico City, Mexico.
36. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. Dec 2007;23(12):1505-1514. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18160008.
37. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. Aug 23 2008;372(9639):646-655. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18722869.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

38. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. Jul 31 2008;22(12):1389-1397. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614861.
39. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS Res Ther*. 2008;5:5. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18373851.
40. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. Sep 5 2009;374(9692):796-806. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19647866.
41. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. Jun 30 2012;379(9835):2429-2438. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748590.
42. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. Jun 30 2012;379(9835):2439-2448. Available at http://www.ncbi.nlm.nih.gov/pubmed/22748591.
43. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials*. Jul-Aug 2012;13(4):228-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/22849964.
44. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. Nov 2013;13(11):927-935. Available at http://www.ncbi.nlm.nih.gov/pubmed/24074642.
45. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis*. Apr 15 2003;36(8):1070-1073. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12684922.
46. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. Jan 15 2006;42(2):283-290. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16355343.
47. Gervasoni C, Meraviglia P, Landonio S, et al. Low body weight in females is a risk factor for increased tenofovir exposure and drug-related adverse events. *PLoS One*. 2013;8(12):e80242. Available at http://www.ncbi.nlm.nih.gov/pubmed/24312465.
48. Moore R, Keruly J, Gallant J. Tenofovir and renal dysfunction in clinical practice. Presented at: 14th Conference on Retrovirus and Opportunistic Infections. 2007. Los Angeles, CA.
49. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr*. Nov 1 2006;43(3):278-283. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17079992.
50. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. Jan 1 2008;197(1):102-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171292.
51. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther*. Feb 2008;83(2):265-272. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597712.
52. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS*. Sep 24 2009;23(15):1971-1975. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19696652.
53. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribald) [package insert]. Gilead. 2015. Available at

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http://www.gilead.com/~/media/files/pdfs/medicines/hiv/stribild/stribild_pi.pdf. Accessed July 1, 2016.

54. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. Oct 15 2010;51(8):963-972. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20828304.
55. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis*. Jun 2011;203(12):1791-1801. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21606537.
56. Perrot S, Aslangul E, Szwebel T, Caillat-Vigneron N, Le Jeunne C. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *J Clin Rheumatol*. Mar 2009;15(2):72-74. Available at http://www.ncbi.nlm.nih.gov/pubmed/19265350.
57. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the *HIV Med*icine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Nov 1 2014;59(9):e96-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/25234519.
58. Pappa K, Baumgarten A, Felizarta F, et al. Dolutegravir (DTG) + abacavir/lamivudine once daily superior to tenofovir/emtricitabine/efavirenz in treatment naive HIV subjects: 144-week results from SINGLE (ING114467). Presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). 2014. Washington D.C.
59. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. Mar 31 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24698485.
60. Feinberg J, Clotet B, Khuong-Josses MA, et al. Once-daily dolutegravir (DTG) is superior to darunavir/ritonavir (DRV/r) in antiretroviral-naive adults: 48 week results from FLAMINGO (ING114915). Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy. 2013. Denver, CO.
61. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19490. Available at http://www.ncbi.nlm.nih.gov/pubmed/25393999.
62. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. Mar 1 2014;65(3):e118-120. Available at http://www.ncbi.nlm.nih.gov/pubmed/24256630.
63. Clumeck N, Molina J, Henry K, Gathe J, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF (STB) has durable efficacy and differentiated safety compared to atazanavir boosted by ritonavir plus emtricitabine/tenofovir DF at week 144 in treatment-naive HIV-1 infected patients. Presented at: 14th European AIDS Conference. 2013. Brussels, Belgium.
64. Elvitegravir/cobicistat/emtricitabine/tenofovir (Genvoya) [package insert]. Gilead. 2016. Available at https://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf?la=en. Accessed July 1, 2016.
65. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther*. Jan 2009;85(1):64-70. Available at http://www.ncbi.nlm.nih.gov/pubmed/18815591.
66. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr*. Sep 1 2012;61(1):32-40. Available at http://www.ncbi.nlm.nih.gov/pubmed/22732469.
67. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. May 1 2013;63(1):77-85. Available at http://www.ncbi.nlm.nih.gov/pubmed/23412015.
68. Raltegravir (Isentress) [package insert] Food and Drug Administration. 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022145s035,203045s012,205786s003lbl.pdf. Accessed July 1, 2016.
69. Snedecor SJ, Khachatryan A, Nedrow K, et al. The prevalence of transmitted resistance to first-generation non-nucleoside reverse transcriptase inhibitors and its potential economic impact in HIV-infected patients. *PLoS One*. 2013;8(8):e72784. Available at http://www.ncbi.nlm.nih.gov/pubmed/23991151.
70. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in

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treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. May 1 2012;60(1):33-42. Available at http://www.ncbi.nlm.nih.gov/pubmed/22343174.

71. Rilpivirine (Edurant) [package insert]. 2015. Available at http://www.edurant.com/shared/product/Edurant/EDURANT-PI.pdf. July 1, 2016
72. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. Apr 5 2011;154(7):445-456. Available at http://www.ncbi.nlm.nih.gov/pubmed/21320923.
73. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. Mar 27 2013;27(6):939-950. Available at http://www.ncbi.nlm.nih.gov/pubmed/23211772.
74. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. *AIDS*. Apr 24 2014;28(7):989-997. Available at http://www.ncbi.nlm.nih.gov/pubmed/24508782.
75. Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. Feb 7 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24522178.
76. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. Jul 1 2014;161(1):1-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/24979445.
77. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19512. Available at http://www.ncbi.nlm.nih.gov/pubmed/25394021.
78. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *J Int AIDS Soc*. 2014;17:19214. Available at http://www.ncbi.nlm.nih.gov/pubmed/25192857.
79. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. Jan 25 2002;16(2):299-300. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11807320.
80. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21311113.
81. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther*. 2011;16(3):339-348. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21555816.
82. Monforte AD, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. *AIDS*. Jan 28 2013;27(3):407-415. Available at http://www.ncbi.nlm.nih.gov/pubmed/23291539.
83. Orkin C, Dejesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med*. Jan 2013;14(1):49-59. Available at http://www.ncbi.nlm.nih.gov/pubmed/23088336.
84. Trottier B, Machouf N, Thomas R, et al. Abacavir/lamivudine fixed-dose combination with ritonavir-boosted darunavir: a safe and efficacious regimen for HIV therapy. *HIV Clin Trials*. Nov-Dec 2012;13(6):335-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/23195671.
85. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis*. Jun 15 2015;60(12):1842-1851. Available at http://www.ncbi.nlm.nih.gov/pubmed/25767256.
86. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. Mar 1 2010;53(3):323-332. Available at

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20032785.

87. Smith KY, Tierney C, Mollan K, et al. Outcomes by sex following treatment initiation with atazanavir plus ritonavir or efavirenz with abacavir/lamivudine or tenofovir/emtricitabine. *Clin Infect Dis*. Feb 2014;58(4):555-563. Available at http://www.ncbi.nlm.nih.gov/pubmed/24253247.

88. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. *J Infect Dis*. Jul 2013;208(1):32-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/23532097.

89. Gallant JE, Koenig E, Andrade-Villanueva JF, et al. Brief report: cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results. *J Acquir Immune Defic Syndr*. Jul 1 2015;69(3):338-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/26181707.

90. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther*. Apr 2016;99(4):363-369. Available at http://www.ncbi.nlm.nih.gov/pubmed/26417955.

91. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS*. May 31 2007;21(9):1215-1218. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17502736.

92. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS*. Aug 24 2011;25(13):1671-1673. Available at http://www.ncbi.nlm.nih.gov/pubmed/21716074.

93. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis*. Nov 2012;55(9):1262-1269. Available at http://www.ncbi.nlm.nih.gov/pubmed/22820542.

94. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis*. May 1 2013;207(9):1359-1369. Available at http://www.ncbi.nlm.nih.gov/pubmed/23382571.

95. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis*. Nov 2012;55(9):1270-1272. Available at http://www.ncbi.nlm.nih.gov/pubmed/22820540.

96. Cobicistat (Tybost) [package insert]. Gilead. 2016. Available at http://www.gilead.com/~/media/Files/pdfs/medicines/hiv/tybost/tybost_pi.pdf. Accessed July 1, 2016.

97. Darunavir/cobicistat (Prezcobix) [package insert]. Janssen. 2016. Available at https://www.prezcobix.com/sites/www.prezcobix.com/files/prescribing-information-prezcobix.pdf. Accessed July 1, 2016.

98. Tashima K, Crofoot G, Tomaka FL, et al. Phase IIIb, open-label single-arm trial of darunavir/cobicistat (DRV/COBI): Week 48 subgroup analysis of HIV-1-infected treatment-nave adults. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19772. Available at http://www.ncbi.nlm.nih.gov/pubmed/25397516.

99. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. Nov 29 2014;384(9958):1942-1951. Available at http://www.ncbi.nlm.nih.gov/pubmed/25103176.

100. Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS*. Nov 13 2011;25(17):2113-2122. Available at http://www.ncbi.nlm.nih.gov/pubmed/21857490.

101. Bedimo RJ, Drechsler H, Jain M, et al. The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health. *PLoS One*. 2014;9(8):e106221. Available at http://www.ncbi.nlm.nih.gov/pubmed/25170938.

102. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. Jul 2014;14(7):572-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/24783988.

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What Not to Use (Last updated March 27, 2012; last reviewed March 27, 2012)

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 Regimens Not Recommended

Monotherapy with nucleoside reverse transcriptase inhibitor (NRTI). Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission (PMTCT), zidovudine (ZDV) monotherapy is not recommended but might be considered in certain unusual circumstances in women with HIV RNA <1,000 copies/mL, although the use of a potent combination regimen is preferred. (See Perinatal Guidelines,[1] available at http://aidsinfo.nih.gov.)

Single-drug treatment regimens with a ritonavir (RTV)-boosted protease inhibitor (PI), either lopinavir (LPV),[2] atazanavir (ATV),[3] or darunavir (DRV)[4-5] are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-NRTI regimens. These regimens **are not recommended** because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens **(AI)**.[6]

Triple-NRTI regimens. In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) **(BI)** and possibly lamivudine/zidovudine + tenofovir (3TC/ZDV + TDF) **(BII) should not be used** because of suboptimal virologic activity[7-9] or lack of data **(AI)**.

Antiretroviral Components Not Recommended

Atazanavir (ATV) + indinavir (IDV). Both of these PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** for combined use **(AIII)**.

Didanosine (ddI) + stavudine (d4T). The combined use of ddI and d4T as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis.[10-13] This combination has been implicated in the deaths of several HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis.[14] Therefore, the combined use of ddI and d4T **is not recommended (AII)**.

Didanosine (ddI) + tenofovir (TDF). Use of ddI + TDF may increase ddI concentrations[15] and serious ddI-associated toxicities including pancreatitis and lactic acidosis.[16-17] These toxicities may be lessened by ddI dose reduction. The use of this combination has also been associated with immunologic nonresponse or CD4 cell decline despite viral suppression,[18-19] high rates of early virologic failure,[20-21] and rapid selection of resistance mutations.[20-22] Because of these adverse outcomes, this dual-NRTI combination **is not generally recommended (AII)**. Clinicians caring for patients who are clinically stable on regimens containing ddI + TDF should consider altering the NRTIs to avoid this combination.

Two-non-nucleoside reverse transcriptase inhibitor (2-NNRTI) combinations. In the 2NN trial, ARV-naive participants were randomized to receive once- or twice-daily nevirapine (NVP) versus efavirenz (EFV) versus EFV plus NVP, all combined with d4T and 3TC.[23] A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both EFV and NVP may induce metabolism of etravirine (ETR), which leads to reduction in ETR drug exposure.[24] Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

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Efavirenz (EFV) in first trimester of pregnancy and in women with significant childbearing potential. EFV use was associated with significant teratogenic effects in nonhuman primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to EFV.[25-26] EFV **should be avoided** in pregnancy, particularly during the first trimester, and in women of childbearing potential who are trying to conceive or who are not using effective and consistent contraception **(AIII)**. If no other ARV options are available for the woman who is pregnant or at risk of becoming pregnant, the provider should consult with a clinician who has expertise in both HIV infection and pregnancy. (See Perinatal Guidelines,[1] available at http://aidsinfo.nih.gov.)

Emtricitabine (FTC) + lamivudine (3TC). Both of these drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo*, as seen with other dual-cytidine analog combinations.[27] These two agents **should not be used** as a dual-NRTI combination **(AIII)**.

Etravirine (ETR) + unboosted PI. ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established[24] **(AII)**.

Etravirine (ETR) + ritonavir (RTV)-boosted atazanavir (ATV) or fosamprenavir (FPV). ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established[24] **(AII)**.

Etravirine (ETR) + ritonavir (RTV)-boosted tipranavir (TPV). RTV-boosted TPV significantly reduces ETR concentrations. These drugs **should not be coadministered**[24] **(AII)**.

Nevirapine (NVP) initiated in ARV-naive women with CD4 counts >250 cells/mm^3 or in ARV-naive men with CD4 counts >400 cells/mm^3. Greater risk of symptomatic hepatic events, including serious and life-threatening events, has been observed in these patient groups. NVP **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk.[28-30] Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy (ART) can be safely switched to NVP.[31]

Unboosted darunavir (DRV), saquinavir (SQV), or tipranavir (TPV). The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV. Therefore, use of these agents as part of a combination regimen **without RTV is not recommended (AII)**.

Stavudine (d4T) + zidovudine (ZDV). These two NRTIs **should not be used** in combination because of antagonism demonstrated *in vitro*[32] and *in vivo*[33] **(AII)**.

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Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 1 of 2)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naive patients. • Other triple-NRTI regimens have not been evaluated.	• ABC/ZDV/3TC **(BI)** and possibly TDF + ZDV/3TC **(BII)** in patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• No exception
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR.	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks **(BIII)**
FTC + 3TC (AIII)	• Similar resistance profiles • No potential benefit	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception

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Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)

	Rationale	Exception
NVP in ARV-naive women with CD4 count >250 cells/mm^3 or men with CD4 count >400 cells/mm^3 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (AII)	• Inadequate bioavailability	• No exception

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

References

1. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
2. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS*. 2008;22(3):385-393.
3. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA*. 2006;296(7):806-814.
4. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS*. 2010;24(2):223-230.
5. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. 2010;24(15):2365-2374.
6. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis*. 1999;180(3):659-665.
7. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis*. 2005;192(11):1921-1930.
8. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr*. 2006;43(3):284-292.
9. Barnas D, Koontz D, Bazmi H, et al. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther*. 2010;15(3):437-441.
10. Moore RD, Wong WM, Keruly JC, et al. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudine and hydroxyurea. *AIDS*. 2000;14(3):273-278.
11. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349(24):2293-2303.
12. Boubaker K, Flepp M, Sudre P, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis*. 2001;33(11):1931-1937.
13. Coghlan ME, Sommadossi JP, Jhala NC, et al. Symptomatic lactic acidosis in hospitalized antiretroviral-treated patients with human immunodeficiency virus infection: a report of 12 cases. *Clin Infect Dis*. 2001;33(11):1914-1921.
14. FDA FaDA. Caution issued for HIV combination therapy with Zerit and Videx in pregnant women. *HIV Clin*. 2001;13(2):6.

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15. Kearney BP, Sayre JR, Flaherty JF, et al. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. *J Clin Pharmacol*. 2005;45(12):1360-1367.

16. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis*. 2003;36(8):1082-1085.

17. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with coadministration of didanosine and tenofovir in HIV-infected adults. *Lancet*. 2004;364(9428):65-67.

18. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. 2005;19(6):569-575.

19. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis*. 2005;41(6):901-905.

20. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS*. 2005;19(2):213-215.

21. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS*. 2005;19(11):1183-1188.

22. Podzamczer D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther*. 2005;10(1):171-177.

23. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363(9417):1253-1263.

24. Tibotec, Inc. Intelence (package insert) 2009.

25. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2):299-300.

26. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989 - 31 January 2007. 2007; http://www.APRegistry.com.

27. Bethell R, Adams J, DeMuys J, et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California. Abstract 138.

28. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5):538-539.

29. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. 2005;191(6):825-829.

30. Boehringer Ingelheim. Dear Health Care Professional Letter. *Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine)* 2004.

31. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. 2009;23(13):1689-1699.

32. Hoggard PG, Kewn S, Barry MG, et al. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation *in vitro*. *Antimicrob Agents Chemother*. 1997;41(6):1231-1236.

33. Havlir DV, Tierney C, Friedland GH, et al. *In vivo* antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis*. 2000;182(1):321-325.

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Management of the Treatment-Experienced Patient

Virologic Failure (Last updated April 8, 2015; last reviewed April 8, 2015)

Panel's Recommendations

- Assessing and managing a patient 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 or drug-food interactions, drug tolerability, HIV RNA and CD4 T lymphocyte (CD4) cell count trends over time, treatment history, and prior and current drug-resistance testing 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—although it may not detect previously selected resistance mutations—can still provide useful information to guide therapy **(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 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 treatment history and drug-resistance testing results and/or the drug's 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, maximal virologic suppression is not possible. In this case, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression.
- 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.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases 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 currently recommended for initial therapy of HIV-infected patients have a high likelihood of achieving and maintaining plasma HIV RNA levels 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 often develop resistance mutations to one or more components of their regimen. Based on surveillance data for HIV patients in care in selected cities in the United States in 2009, an estimated 89% of the patients were receiving ART, of whom 72% had viral loads <200 copies/mL.[1] Many patients with detectable viral loads are non-adherent to treatment. 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 these individuals.

Virologic Response Definitions

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

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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 will take longer than others to suppress HIV RNA levels.

Virologic rebound: Confirmed HIV RNA ≥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

ART Treatment Goals and Virologic Responses

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.[2]

Viremia "blips"—defined by viral suppression followed by an isolated detectable HIV RNA level and subsequent return to undetectable levels—are not usually associated with subsequent virologic failure.[3] In contrast, there is controversy regarding the clinical implications of persistent HIV RNA levels between the LLOD and <200 copies/mL in patients on ART. Furthermore, viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than PCR-based viral load platforms used in the past.[4-6] 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 to >200 copies/mL.[7] 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 to 199 copies/mL.[8,9] However, other studies have suggested that viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound[10,11] and can be associated with the evolution of drug resistance.[12]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[13] This association is particularly common when HIV RNA levels are >500 copies/mL.[14] Therefore, persistent plasma HIV RNA levels ≥200 copies/mL should be 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 accounted for 28% to 40% of virologic failure and regimen discontinuations.[15,16] Presence of pre-existing (transmitted) drug resistance may also be the cause of virologic failure.[17] Virologic failure may be associated with both patient- and regimen-related factors, as listed below:

- **Patient-Related Factors**
  - Higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
  - Lower pretreatment or nadir CD4 T lymphocyte (CD4) cell count (depending on the specific regimen used)
  - Comorbidities that may affect adherence (e.g., active substance abuse, psychiatric disease, neurocognitive deficits)
  - Presence of drug-resistant virus, either transmitted or acquired

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- Prior treatment failure
- Incomplete medication adherence and missed clinic appointments
- Interruption of or intermittent access to ART

- **ARV Regimen-Related Factors**
  - Drug adverse effects
  - Suboptimal pharmacokinetics (variable absorption, metabolism, or possibly penetration into reservoirs)
  - Suboptimal virologic potency
  - Reduced efficacy because of a patient's prior exposure to suboptimal regimens (e.g., functional monotherapy)
  - Food requirements
  - High pill burden and/or dosing frequency
  - Adverse drug-drug interactions with concomitant medications
  - Prescription errors
  - Cost and affordability of ARVs (i.e., may affect a patient's ability to access or continue therapy)

Management of Patients with Virologic Failure

Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment that includes consideration of the factors listed in the Causes of Virologic Failure section above is indicated. Often the causes of virologic failure can be identified, but in some cases, the causes are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth:

- **Suboptimal Adherence.** Assess the patient's adherence to the regimen. Identify and address the underlying cause(s) for incomplete adherence (e.g., drug intolerance, difficulty accessing medications, depression, active substance abuse) and, if possible, simplify the regimen (e.g., decrease pill count or dosing frequency). (See Adherence.)
- **Medication Intolerance.** Assess 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. Management strategies to address intolerance in the absence of drug resistance may include:
  - Symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - A switch from one ARV in a regimen to another agent in the same drug class (see the Adverse Effects section)
  - A switch from one drug class to another class (e.g., from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI] or an integrase strand transfer inhibitor [INSTI]), if necessary (see the Adverse Effects section)

- **Pharmacokinetic Issues**
  - Review food requirement for each medication, and assess whether the patient adheres to the requirement.
  - Review the patient's recent history of gastrointestinal symptoms such as vomiting or diarrhea that may result in short-term malabsorption.
  - Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult the Drug Interactions section and tables for common interactions) and, if possible, make appropriate substitutions for ARV agents and/or concomitant medications.
  - Consider therapeutic drug monitoring if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected (see also Exposure-Response

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Relationship and Therapeutic Drug Monitoring).

- **Suspected Drug Resistance.** Perform resistance testing 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 between 500 to 1,000 copies/mL **(BII)**. (See Drug-Resistance Testing.) In some patients, resistance testing should be considered even after treatment interruptions of more than 4 weeks, recognizing 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)**. Evaluate the extent of drug resistance, taking into account the patient's past treatment history and prior resistance-test results. Drug resistance is cumulative; thus, all prior treatment history and resistance test results should be considered when evaluating resistance. Genotypic or phenotypic testing provides information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, PIs, and INSTIs. Additional drug-resistance tests for patients experiencing failure on a fusion inhibitor **(AII)** and viral tropism tests for patients experiencing failure on a CCR5 antagonist **(BIII)** are also available. (See Drug-Resistance Testing.)

Approach to Patients with Confirmed Virologic Failure

Once virologic failure is confirmed, every effort should be made to assess whether suboptimal adherence and drug-drug or drug-food interactions may be contributing to the inadequate virologic response to ART. If virologic failure persists after these issues have been adequately addressed, resistance testing should be performed, and the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations.[18] In addition, several studies have shown that virologic responses to new regimens are greater in individuals with lower HIV RNA levels[10,19] and/or higher CD4 cell counts at the time of regimen changes.[10,19] Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression;[20,21] therefore, this strategy is **not** recommended **(AI)**. See Discontinuation or Interruption of Antiretroviral Therapy.

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 drug treatment history, resistance testing, or the mechanistic action of a new drug class **(AI)**.[10,22-31] Despite drug resistance, some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen,[21] while other agents (e.g., enfuvirtide [T20], NNRTIs, the INSTI raltegravir [RAL]) likely will not.[32-34] Using a "new" drug that a patient has never used previously does not ensure that the drug will be fully active; there is potential for cross-resistance, particularly among drugs from the same class. In addition, 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. Therefore, both treatment history and prior and current drug-resistance test results must be considered when designing a new regimen. When designing a new ART regimen, drug potency and viral susceptibility are more important factors to consider than the number of component drugs.

In general, patients who receive at least three active drugs, selected based on a review of the patient's treatment history and past and most current drug-resistance test results, experience better and more sustained virologic response than those receiving fewer active drugs in the regimen.[23,24,26,27,35,36] However, there are increasing data in treatment-naive and treatment-experienced patients showing that an active pharmacokinetically enhanced PI plus one other active drug or several partially active drugs will effectively reduce viral load in most patients.[37-40] Active drugs are ARVs that, based on resistance test results and treatment history, are expected to have antiviral activity equivalent to that 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. The activity of a given drug must be uniquely defined for each patient. 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 tipranavir, and dolutegravir [DTG]) An active drug may also be one with unique mechanisms of action (e.g.,

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the fusion inhibitor T20, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus). In the presence of certain drug resistance mutations, some ARVs such as DTG, ritonavir-boosted DRV, and ritonavir-boosted lopinavir (LPV/r) need to be given twice daily instead of once daily to achieve higher drug concentrations necessary to be active against the less sensitive virus.[41,42]

Addressing Detectable Viral Load in Different Clinical Situations

- **HIV RNA above the LLOD and <200 copies/mL.** Confirm that levels remain above the LLOD and assess adherence, drug-drug interactions (including those with over-the-counter products and supplements), and drug-food interactions. Patients with HIV RNA typically below the LLOD with transient increases in HIV RNA (i.e., blips) do not require a change in treatment **(AII)**.[5] Although there is no consensus on how to manage patients with persistent HIV RNA levels above the LLOD and <200 copies/mL, the risk of emerging resistance is believed to be relatively low. Therefore, these patients should maintain on their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes in ART in the future **(AIII)**.
- **HIV RNA ≥200 and <1,000 copies/mL.** Confirm that HIV RNA levels remain in this range and assess adherence and potential drug-drug interactions (including those with over-the-counter products and supplements) and drug-food interactions. In contrast to patients with HIV RNA levels persistently <200 copies/mL, those with levels persistently ≥200 copies/mL often develop drug resistance, particularly with HIV RNA levels >500 copies/mL.[8,9] Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as virologic failure, and resistance testing should be attempted, particularly if HIV RNA >500 copies/mL. When resistance testing can successfully be performed and no resistance is detected, manage the patient as outlined below in the section on **HIV RNA >1,000 copies/mL and <u>no</u> drug resistance identified**. If drug resistance is detected, manage the patient as outlined below in the section on **HIV RNA >1,000 copies/mL and drug resistance identified**. When resistance testing cannot be performed because of low-level viremia, the decision whether to empirically change ARVs should be made on a case-by-case basis.
- **HIV RNA >1,000 copies/mL and <u>no</u> drug resistance identified.** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment to determine the level of adherence and identify any drug-drug and drug-food interactions. Consider the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-non-adherent for more than 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 resume the same regimen. If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen. Two to four weeks after treatment is resumed or started, repeat viral load testing; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain emerges **(CIII)**.
- **HIV RNA >1,000 copies/mL and drug resistance identified.** 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 present and are addressed in the clinical scenarios outlined below.

Management of Virologic Failure in Different Clinical Scenarios

First Regimen Failure

- **Failing an NNRTI plus NRTI regimen.** Patients failing an NNRTI-based regimen often have viral resistance to the NNRTI, with or without lamivudine (3TC) and emtricitabine (FTC) resistance. Although several options are available for these patients, several studies have explored the activity of a pharmacokinetically boosted PI with NRTIs or an INSTI.[43-45] Two of the studies found that regimens containing a ritonavir-boosted PI (PI/r) combined with NRTIs were as active as regimens containing the PI/r

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combined with RAL.[43,45] Two studies also demonstrated higher rates of virologic suppression with use of a PI/r plus NRTIs than with a PI/r alone.[44,45] On the basis of these studies, even patients with NRTI resistance can often be treated with a pharmacokinetically boosted PI plus NRTIs or RAL (AI). Although LPV/r was used in these studies, it is likely that other pharmacokinetically boosted PIs would behave similarly. Although data are limited, the second-generation NNRTI ETR or the other INSTIs (i.e., elvitegravir [EVG] or DTG) combined with a pharmacokinetically boosted PI may also be options in this setting.

- **Failing a pharmacokinetically boosted PI plus NRTI regimen.** In this scenario, most patients will have either no resistance or resistance limited to 3TC and FTC.[46,47] Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. A systematic review of multiple randomized trials of PI/r first-line failure showed that maintaining the same regimen, presumably with efforts to enhance adherence, is as effective as changing to new regimens with or without drugs from new classes.[48] In this setting, resistance testing should be performed along with an assessment of overall adherence and tolerability of the regimen. If the regimen is well tolerated and there are no concerns regarding drug-drug or drug-food interactions, the regimen can be continued with adherence support and viral monitoring. Alternatively, if poor tolerability or interactions may be contributing to virologic failure, the regimen can be modified to include a different pharmacokinetically boosted PI plus NRTIs—even if not all of the NRTIs are fully active—or to a new non-PI-based regimen that includes more than two fully active agents **(AII)**.
- **Failing an INSTI plus NRTI regimen.** Virologic failure with a regimen consisting of RAL plus two NRTIs or with EVG/cobicistat/tenofovir disoproxil fumarate/FTC may be associated with emergent resistance to 3TC and FTC and possibly the INSTI.[49] Viruses with INSTI resistance often have virus still susceptible to DTG.[19] In contrast, persons failing DTG plus two NRTI first-line therapy in clinical trials have not yet been shown to develop phenotypic resistance to DTG.[49] There are no clinical trial data to guide therapy for first-line INSTI failures, although one can likely extrapolate from the data for NNRTI failures. Thus, patients with first-line INSTI failure should respond to a pharmacokinetically boosted PI plus NRTIs **(AII)**. A pharmacokinetically boosted PI plus an INSTI may also be a viable option in patients with no INSTI resistance **(BII)**. In the setting the virus is found to have resistance to RAL and EVG but remains susceptible to DTG, DTG can be used in combination with a pharmacokinetically boosted PI. If no resistance is identified, the patient should be managed as outlined above in the section on virologic failure without resistance.

Second-Line Regimen Failure and Beyond

- **Drug resistance with treatment options allowing for full virologic suppression.** Depending on treatment history and drug-resistance data, one can predict whether or not to have a fully active pharmacokinetically boosted PI to include in future regimens. For example, those who have no documented PI resistance and previously have never been treated with an unboosted PI are likely to harbor virus that is fully susceptible to ARVs in the PI class. In this setting, viral suppression should be achievable using a pharmacokinetically boosted PI combined with either NRTIs or an INSTI—provided the virus is susceptible to the INSTI. If a fully susceptible pharmacokinetically boosted PI is not an option, the new regimen should include at least two, and preferably three, fully active agents, if possible. Drugs to be included in the regimen 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 treatment options allowing for full virologic suppression.** Use of currently available ARVs has resulted in a dramatic decline in the number of patients who have few treatment options because of multi-class drug resistance.[50,51] 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

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function, prevent clinical progression, and minimize increasing resistance to drug classes that may eventually include new drugs that may be important for future regimens. Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T20, EVG or RAL are identified, there is rarely a reason to continue these drugs, as there is little evidence that keeping them in the regimen helps delay disease progression **(BII)**. Moreover, continuing these drugs, in particular INSTIs, may allow for further increasing resistance and 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 benefits.[50,52] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 count increases, reduces the risk of disease progression.[53] Other cohort studies suggest continued immunologic and clinical benefits with even modest reductions in HIV RNA levels.[54,55] However, all 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)**.

Patients with ongoing viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for research studies or expanded access programs or may qualify for single-patient access of an investigational new drug as specified in Food and Drug Administration regulations: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm. Information about these programs may also be available from the sponsoring pharmaceutical manufacturer.

- **Previously treated patient with suspected drug resistance who need care but present with limited information (i.e., incomplete or no self-reported history, medical records, or resistance-testing results).** Every effort should be made to obtain the patient's medical records and prior drug-resistance testing 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 selection of the next regimen. Another strategy is to start two or three drugs predicted to be active on the basis of the patient's treatment history.

Isolated Central Nervous System (CNS) Virologic Failure and New Onset Neurologic Symptoms

Presentation with new-onset CNS signs and symptoms has been reported as a rare form of 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.[56,57] Clinical evaluation frequently shows abnormalities on MRI brain imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis. When available, measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most patients, evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF, if available, 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 be useful to consider CNS pharmacokinetics in drug selection **(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[58-60] **(CIII)**. This "neurosymptomatic" CNS viral escape should be distinguished from: (1) other CNS infections that can induce a transient increase in CSF HIV RNA (e.g., herpes zoster[61]), (2) incidental detection of asymptomatic mild CSF HIV RNA elevation likely equivalent to plasma blips,[62] or (3) relatively common chronic, usually mild, neurocognitive impairment in HIV-infected patients without evidence of CNS viral breakthrough.[63] None of these latter conditions currently warrant a change in ART.[64]

Summary

In 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 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, treatment history, and

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drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider use of investigational agents through participation in clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

References

1. Blair JM, Fagan JL, Frazier EL, et al. Behavioral and clinical characteristics of persons receiving medical care for HIV infection - Medical Monitoring Project, United States, 2009. *Morb Mortal Wkly Rep Surveill Summ*. 2014;63 Suppl 5:1-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/24941443.
2. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic analysis of HIV-1 drug resistance at the limit of detection: virus production without evolution in treated adults with undetectable HIV loads. *J Infect Dis*. 2004;189(8):1452-1465. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15073683.
3. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA*. 2005;293(7):817-829. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15713771.
4. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr*. 2009;51(1):3-6. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19247185.
5. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis*. 2009;48(2):260-262. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19113986.
6. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr*. 2010;54(4):442-444. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20611035.
7. Ribaudo H, Lennox J, Currier J, al e. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada, 2009.
8. Antiretroviral Therapy Cohort C. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. 2015;29(3):373-383. Available at http://www.ncbi.nlm.nih.gov/pubmed/25686685.
9. Boillat-Blanco N, Darling KE, Schoni-Affolter F, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antivir Ther*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24964403.
10. Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. *Lancet Infect Dis*. 2013;13(7):587-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/23664333.
11. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. 2013;57(10):1489-1496. Available at http://www.ncbi.nlm.nih.gov/pubmed/23946221.
12. Taiwo B, Gallien S, Aga S, al e. HIV drug resistance evolution during persistent near-target viral suppression. *Antiviral Therapy* 2010;15:A38.
13. Aleman S, Soderbarg K, Visco-Comandini U, Sitbon G, Sonnerborg A. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS*. 2002;16(7):1039-1044. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11953470.
14. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004;18(7):981-989. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15096800.
15. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active

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antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS*. 2000;14(5):499-507. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10780712.

16. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS*. 2001;15(2):185-194. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11216926.
17. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. 2010;201(5):662-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20102271.
18. Hosseinipour MC, van Oosterhout JJ, Weigel R, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*. 2009;23(9):1127-1134. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19417582.
19. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24446523.
20. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med*. 2003;349(9):837-846. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12944569.
21. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med*. 2001;344(7):472-480. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11172188.
22. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):355-365. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18650513.
23. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med*. 2003;348(22):2186-2195. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12773645.
24. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med*. 2003;348(22):2175-2185. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12637625.
25. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS*. 2007;21(8):533-543. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17711378.
26. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. 2007;369(9568):1169-1178. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17416261.
27. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359(4):339-354. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18650512.
28. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. 2009;23(17):2289-2300. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19710593.
29. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1429-1441. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18832244.
30. Fatkenheuer G, Nelson M, Lazzarin A, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1442-1455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18832245.
31. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-

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naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013;382(9893):700-708. Available at http://www.ncbi.nlm.nih.gov/pubmed/23830355.

32. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis*. 2005;192(9):1537-1544. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16206068.
33. Deeks SG, Lu J, Hoh R, et al. Interruption of enfuvirtide in HIV-1 infected adults with incomplete viral suppression on an enfuvirtide-based regimen. *J Infect Dis*. 2007;195(3):387-391. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205477.
34. Wirden M, Simon A, Schneider L, et al. Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother*. 2009;64(5):1087-1090. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19717396.
35. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet*. 2006;368(9534):466-475. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16890833.
36. Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis*. 2012;12(1):27-35. Available at http://www.ncbi.nlm.nih.gov/pubmed/22015077.
37. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014;14(7):572-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/24783988.
38. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014;384(9958):1942-1951. Available at http://www.ncbi.nlm.nih.gov/pubmed/25103176.
39. Second-Line Study Group, Boyd MA, Kumarasamy N, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet*. 2013;381(9883):2091-2099. Available at http://www.ncbi.nlm.nih.gov/pubmed/23769235.
40. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med*. 2014;371(3):234-247. Available at http://www.ncbi.nlm.nih.gov/pubmed/25014688.
41. Prezista [package insert]. Food and Drug Administration. 2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021976s033_202895s010lbl.pdf. Accessed February 11, 2014.
42. Tivicay [package insert]. Food and Drug Administration. 2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf. Accessed February 11, 2014.
43. Second-Line Study Group, Boyd MA, Kumarasamy N, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet*. 2013;381(9883):2091-2099. Available at http://www.ncbi.nlm.nih.gov/pubmed/23769235.
44. Bunupuradah T, Chetchotisakd P, Ananworanich J, et al. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. *Antivir Ther*. 2012;17(7):1351-1361. Available at http://www.ncbi.nlm.nih.gov/pubmed/23075703.
45. Paton NI, Kityo C, Hoppe A. A pragmatic randomised controlled strategy trial of three second-line treatment options for use in public health rollout programme settings: the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial. Abstract WELBB02.2013. Presented at: 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013). 2013. Kuala Lumpur, Malaysia.
46. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21311113.

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47. Stebbing J, Nathan B, Jones R, et al. Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS*. 2007;21(13):1826-1828. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690587.

48. Zheng Y, Lambert C, Arendt V, Seguin-Devaux C. Virological and immunological outcomes of elvitegravir-based regimen in a treatment-naive HIV-2-infected patient. *AIDS*. 2014;28(15):2329-2331. Available at http://www.ncbi.nlm.nih.gov/pubmed/25313590.

49. White KL, Raffi F, Miller MD. Resistance analyses of integrase strand transfer inhibitors within phase 3 clinical trials of treatment-naive patients. *Viruses*. 2014;6(7):2858-2879. Available at http://www.ncbi.nlm.nih.gov/pubmed/25054884.

50. De Luca A, Dunn D, Zazzi M, et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis*. 2013;207(8):1216-1220. Available at http://www.ncbi.nlm.nih.gov/pubmed/23315324.

51. Paquet AC, Solberg OD, Napolitano LA, et al. A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. *Antivir Ther*. 2014;19(4):435-441. Available at http://www.ncbi.nlm.nih.gov/pubmed/24518099.

52. Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS*. 1999;13(7):797-804. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10357378.

53. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. 2000;14(18):2857-2867. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153667.

54. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. 2004;364(9428):51-62. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15234856.

55. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr*. 2004;37(1):1147-1154. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15319674.

56. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis*. 2010;50(5):773-778. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20100092.

57. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS*. 2012;26(14):1765-1774. Available at http://www.ncbi.nlm.nih.gov/pubmed/22614889.

58. Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Top Antivir Med*. 2011;19(4):137-142. Available at http://www.ncbi.nlm.nih.gov/pubmed/22156215.

59. Letendre SL, Mills AM, Tashima KT, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. *Clin Infect Dis*. 2014;59(7):1032-1037. Available at http://www.ncbi.nlm.nih.gov/pubmed/24944232.

60. Calcagno A, Di Perri G, Bonora S. Pharmacokinetics and pharmacodynamics of antiretrovirals in the central nervous system. *Clin Pharmacokinet*. 2014;53(10):891-906. Available at http://www.ncbi.nlm.nih.gov/pubmed/25200312.

61. Moling O, Rossi P, Rimenti G, Vedovelli C, Mian P. Varicella-zoster virus meningitis and cerebrospinal fluid HIV RNA. *Scand J Infect Dis*. 2001;33(5):398-399. Available at http://www.ncbi.nlm.nih.gov/pubmed/11440237.

62. Eden A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis*. 2010;202(12):1819-1825. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21050119.

63. Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011;17(1):3-16. Available at http://www.ncbi.nlm.nih.gov/pubmed/21174240.

64. Ellis RJ, Letendre S, Vaida F, et al. Randomized trial of central nervous system-targeted antiretrovirals for HIV-associated neurocognitive disorder. *Clin Infect Dis*. 2014;58(7):1015-1022. Available at http://www.ncbi.nlm.nih.gov/pubmed/24352352.

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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 Summary and Recommendations
• Morbidity and mortality from several AIDS and non-AIDS conditions are increased in HIV-infected individuals 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 none 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, 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 HIV-infected individuals 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 HIV-infected individuals 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 recently HIV-infected individuals 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, HIV-infected individuals with 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

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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 HIV-infected individuals 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

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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 HIV-infected individuals. Thus, clinical monitoring with immune activation or inflammatory markers is **not currently recommended** **(AII)**. The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities such as hypertension, hyperlipidemia, and diabetes **(AII)**.

References

1. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med*. 2011;62:141-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/21090961.
2. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS*. 2001;15(11):1369-1377. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11504958.
3. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. 2009;48(6):787-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/19193107.
4. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. *AIDS*. 2010;24(12):1867-1876. Available at http://www.ncbi.nlm.nih.gov/pubmed/20467286.
5. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. Available at http://www.ncbi.nlm.nih.gov/pubmed/17205456.
6. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230. Available at http://www.ncbi.nlm.nih.gov/pubmed/23323898.
7. Engsig FN, Zangerle R, Katsarou O, et al. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. *Clin Infect Dis*. 2014;58(9):1312-1321. Available at http://www.ncbi.nlm.nih.gov/pubmed/24457342.
8. Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration{dagger}. *Int J Epidemiol*. 2012;41(2):433-445. Available at http://www.ncbi.nlm.nih.gov/pubmed/22493325.
9. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18427202.
10. Achhra AC, Amin J, Law MG, et al. Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients. *AIDS*. 2010;24(12):1877-1886. Available at http://www.ncbi.nlm.nih.gov/pubmed/20588170.
11. Smurzynski M, Wu K, Benson CA, Bosch RJ, Collier AC, Koletar SL. Relationship between CD4+ T-cell counts/HIV-1 RNA plasma viral load and AIDS-defining events among persons followed in the ACTG longitudinal linked randomized trials study. *J Acquir Immune Defic Syndr*. 2010;55(1):117-127. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20622677.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

12. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. 2010;51(4):435-447. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20597691.
13. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2011;57(3):205-210. Available at http://www.ncbi.nlm.nih.gov/pubmed/21522014.
14. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641. Available at http://www.ncbi.nlm.nih.gov/pubmed/16908797.
15. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18832878.
16. Young J, Psichogiou M, Meyer L, et al. CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med*. 2012;9(3):e1001194. Available at http://www.ncbi.nlm.nih.gov/pubmed/22448150.
17. Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS*. 2007;21(8):939-946. Available at http://www.ncbi.nlm.nih.gov/pubmed/17457087.
18. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS*. 2005;19(6):569-575. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15802975.
19. Negredo E, Bonjoch A, Paredes R, Puig J, Clotet B. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis*. 2005;41(6):901-905. Available at http://www.ncbi.nlm.nih.gov/pubmed/16107993.
20. Gandhi RT, Zheng L, Bosch RJ, et al. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. *PLoS Med*. 2010;7(8). Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20711481.
21. Hatano H, Strain MC, Scherzer R, et al. Increase in 2-Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial. *The Journal of Infectious Diseases*. 2013;208(9):1436-1442. Available at http://www.ncbi.nlm.nih.gov/pubmed/23975885.
22. Hunt PW, Shulman NS, Hayes TL, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. *Blood*. 2013;121(23):4635-4646. Available at http://www.ncbi.nlm.nih.gov/pubmed/23589670.
23. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. *Proc Natl Acad Sci U S A*. 2009;106(23):9403-9408. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19470482.
24. Cuzin L, Trabelsi S, Delobel P, et al. Maraviroc intensification of stable antiviral therapy in HIV-1-infected patients with poor immune restoration: MARIMUNO-ANRS 145 study. *J Acquir Immune Defic Syndr*. 2012;61(5):557-564. Available at http://www.ncbi.nlm.nih.gov/pubmed/22986949.
25. Buzon MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med*. 2010;16(4):460-465. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20228817.
26. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS*. 2010;24(11):1697-1707. Available at http://www.ncbi.nlm.nih.gov/pubmed/20467288.
27. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361(16):1548-1559. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19828532.
28. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol*. 2013;119:51-83. Available at http://www.ncbi.nlm.nih.gov/pubmed/23886064.
29. Lederman MM, Calabrese L, Funderburg NT, et al. Immunologic failure despite suppressive antiretroviral therapy is related to activation and turnover of memory CD4 cells. *J Infect Dis*. 2011;204(8):1217-1226. Available at

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

http://www.ncbi.nlm.nih.gov/pubmed/21917895.

30. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. 2003;187(10):1534-1543. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12721933.
31. Hunt PW, Sinclair E, Rodriguez B, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. *J Infect Dis*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24755434.
32. Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non-AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment. *J Infect Dis*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24795473.
33. Tien PC, Choi AI, Zolopa AR, et al. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. *J Acquir Immune Defic Syndr*. 2010;55(3):316-322. Available at http://www.ncbi.nlm.nih.gov/pubmed/20581689.
34. Martinez E, D'Albuquerque PM, Llibre JM, et al. Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir. *AIDS*. 2012;26(18):2315-2326. Available at http://www.ncbi.nlm.nih.gov/pubmed/23018438.
35. Lake JE, McComsey GA, Hulgan T, et al. Switch to raltegravir decreases soluble CD14 in virologically suppressed overweight women: the Women, Integrase and Fat Accumulation Trial. *HIV Med*. 2014;15(7):431-441. Available at http://www.ncbi.nlm.nih.gov/pubmed/24506429.
36. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis*. 2014;58(4):588-595. Available at http://www.ncbi.nlm.nih.gov/pubmed/24253250.
37. O'Brien M, Montenont E, Hu L, et al. Aspirin attenuates platelet activation and immune activation in HIV-infected subjects on antiretroviral therapy: a pilot study. *J Acquir Immune Defic Syndr*. 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23406976.

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Regimen Switching in the Setting of Virologic Suppression (Last updated Jan. 17, 2016; last reviewed July 14, 2016)

Panel's Recommendations
• Advances in antiretroviral (ARV) treatment and a better understanding of HIV drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations. • The fundamental principle of regimen switching is to maintain viral suppression without jeopardizing future treatment options **(AI)**. • It is critical to review a patient's full ARV history, including virologic responses, past ARV-associated toxicities, and cumulative resistance test results, if available, before selecting a new ART regimen **(AI)**. • Adverse events, the availability of ARVs with an improved safety profile, 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)**. • Consultation with an HIV specialist should be considered when considering a regimen switch for a patient with a history of resistance to one or more drug classes **(BIII)**. • More intensive monitoring to assess tolerability, viral suppression, adherence, and laboratory changes 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 HIV-infected patients are able to achieve and maintain HIV viral suppression. Furthermore, advances in treatment and a better understanding of drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations (see below). When considering such a switch, clinicians must consider several key principles to maintain viral suppression while addressing concerns with the current regimen.

Reasons to Consider Regimen Switching in the Setting of Viral Suppression

- To simplify the regimen by reducing pill burden and dosing frequency
- To enhance tolerability and decrease short- or long-term toxicity (see Adverse Events of Antiretroviral Agents and Table 15 for more in-depth discussion)
- To prevent or mitigate drug-drug interactions (see Drug Interactions)
- To eliminate food or fluid requirements
- To allow for optimal use of ART during pregnancy or should pregnancy occur (see Perinatal Guidelines)[1]
- To reduce costs (see Cost Considerations and Antiretroviral Therapy)
- To switch from frequent parenteral administration of enfuvirtide to an oral agent that is better tolerated

General Principles of Regimen Switching

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.

The review of a patient's full antiretroviral (ARV) history—including virologic responses, past ARV-associated toxicities, and cumulative resistance test results (if available)—is warranted before any treatment switch **(AI)**.

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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.

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 not detected in the patient's most recent resistance test. If 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)- or 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 non-nucleoside reverse transcriptase inhibitor (NNRTI) or an elvitegravir (EVG)- or raltegravir (RAL)-containing regimen, resistance to these drugs can also be assumed because these drugs generally have a lower barrier to resistance. 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 as active against potential resistant virus as the suppressive regimen. 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.

A commercially available test amplifies viral DNA in whole blood samples to detect the presence of archived resistance mutations in patients with suppressed HIV RNA. Its value in clinical practice is still being evaluated (see Drug-Resistance Testing).

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

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

Strategies with Good Supporting Evidence

Within-class switches prompted by adverse events or the availability of in-class ARVs that offer a better safety profile, reduced dosing frequency, 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 efavirenz (EFV) to rilpivirine (RPV),[2] from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF),[3] from raltegravir (RAL) to elvitegravir/cobicistat (EVG/c)[4] or dolutegravir (DTG), from ritonavir-boosted protease inhibitors (PIs/r) to PIs coformulated with cobicistat (PIs/c), or from boosted atazanavir (ATV/c or ATV/r) to unboosted ATV (when used with abacavir [ABC]/3TC).[5-7]

Between-class switches generally maintain viral suppression provided there is no resistance to the other components of the regimen. Some examples of between-class switch strategies are replacing a boosted PI with rilpivirine (RPV),[8] or replacing an NNRTI or a boosted PI with an integrase strand transfer inhibitor (INSTI).[9,10] However, such switches should be avoided if there is any doubt about the activity of the other agents in the regimen.

RTV-Boosted PI plus 3TC/FTC

There is growing evidence that a boosted PI-based regimen plus 3TC can maintain virologic suppression in ART-naive individuals without baseline resistance mutations[11] and in patients with sustained viral suppression.[12] Examples of such regimens include lopinavir/ritonavir (LPV/r) plus 3TC[12] and atazanavir/ritonavir (ATV/r) plus 3TC.[13] A study evaluating darunavir/ritonavir (DRV/r) plus 3TC is currently underway. A ritonavir-boosted PI plus 3TC may be a reasonable option when the use of TDF, TAF, or ABC is contraindicated or not desirable.

Strategies under Evaluation

Several strategies for switching regimens (described below) in patients with viral suppression are under investigation. These strategies cannot yet be recommended under most circumstances or at all until further

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evidence is available. If used, patients should be closely monitored to assure viral suppression is maintained.

RTV-Boosted PI plus INSTI

The combination of a boosted PI with an INSTI (DRV/r plus RAL) has been studied in ART-naive patients. At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the proportion of patients achieving viral suppression. However, in patients with low pretreatment CD4 T lymphocyte counts (<200 cells/mm^3) and high viral loads (>100,000 copies/mL), DRV/r plus RAL was inferior to DRV/r plus TDF/FTC.[14] The efficacy of switching to DRV/r plus RAL in virologically suppressed patients with no resistance to either DRV or RAL has not been explored. In another study, virologically suppressed patients switched to a regimen consisting of ATV/r plus RAL or ATV/r plus TDF/FTC. This regimen switch was associated with higher rates of virologic failure and treatment discontinuations than switching to ATV/r plus TDF/FTC.[15] A regimen consisting of ATV/r plus RAL cannot currently be recommended.

EVG/c/TAF/FTC plus DRV

The single-tablet regimen EVG/c/TAF/FTC plus DRV has shown promising results as a simplification strategy in patients with complicated rescue regimens.[16] A recent study enrolled 135 virologically suppressed patients who were receiving DRV-containing ART and had resistance to ≥2 ARV drug classes, but no INSTI resistance. The patients were then switched to a regimen of EVG/c/TAF/FTC plus DRV. At week 24, 97% of the patients maintained virologic suppression. The pill burden was reduced from an average of five tablets to two tablets. Currently, however, there is insufficient evidence to support this regimen switch other than in a well-controlled clinical trial or in special circumstances.

Dolutegravir plus 3TC or FTC

In a small (20-patient), single-arm study of DTG plus 3TC for ART-naive patients, all patients achieved and maintained viral suppression at 24 weeks.[17] A clinical trial is underway to evaluate the role of this regimen as maintenance therapy in virologically suppressed patients who have no evidence of NRTI, INSTI, or PI resistance. Currently, however, there is insufficient evidence to support use of this regimen other than in a well-controlled clinical trial.

Strategies Not Recommended

RTV-Boosted PI Monotherapy

The strategy of switching virologically suppressed patients 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 slightly lower rates than standard therapy that includes 2 NRTIs.[18,19] Low-level viremia, generally without the emergence of PI resistance, appears to be more common with monotherapy. In most studies, resumption of NRTIs in patients experiencing low-level viral rebound has led to re-suppression.[20-23]

On the basis of the results from these studies, PI/r monotherapy should generally be avoided **(BI)**. No clinical trials evaluating the use of coformulated cobicistat-boosted PIs as monotherapy or comparing available PI/r monotherapy regimens have been conducted.

Switching to Maraviroc

Co-receptor usage in virologically suppressed patients can be determined from proviral DNA obtained from peripheral blood mononuclear cells. If this testing identifies R5-tropic virus, a component of the patient's regimen may potentially be switched to maraviroc (MVC).[24,25] However, although the use of MVC after DNA tropism testing has potential, this strategy cannot be recommended until more data from larger clinical studies are available (see Co-receptor Tropism Assays).

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Monitoring after Treatment Changes

After a treatment switch, patients should be evaluated more closely for several months (i.e., 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). The purpose of more intensive monitoring is to assess medication tolerance and conduct targeted laboratory testing if the patient had pre-existing laboratory abnormalities or there are potential concerns with the new regimen. For example, if lipid abnormalities were present and/or were a reason for the ARV change, or if it is a concern with the new regimen, fasting cholesterol subsets and triglycerides should be assessed within 3 months after the change in therapy. In the absence of any new complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis (see Laboratory Testing for Initial Assessment and Monitoring of HIV-Infected Patients on Antiretroviral Therapy).

References

1. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed June 15, 2016.
2. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials*. Sep-Oct 2013;14(5):216-223. Available at http://www.ncbi.nlm.nih.gov/pubmed/24144898.
3. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. Apr 2016;3(4):e158-165. Available at http://www.ncbi.nlm.nih.gov/pubmed/27036991.
4. Mills A, Crofoot G, Ortiz R, et al. Switching from twice-daily raltegravir plus tenofovir disoproxil fumarate/emtricitabine to once-daily elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed, HIV-1-infected subjects: 48 weeks data. *HIV Clin Trials*. Mar-Apr 2014;15(2):51-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/24710918.
5. Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. *HIV Clin Trials*. Sep-Oct 2012;13(5):233-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/23134624.
6. Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. *Antivir Ther*. 2010;15(7):993-1002. Available at http://www.ncbi.nlm.nih.gov/pubmed/21041914.
7. Wohl DA, Bhatti L, Small CB, et al. The ASSURE study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. *HIV Med*. Feb 2016;17(2):106-117. Available at http://www.ncbi.nlm.nih.gov/pubmed/26176344.
8. Palella FJ, Jr., Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS*. Jan 28 2014;28(3):335-344. Available at http://www.ncbi.nlm.nih.gov/pubmed/24670520.
9. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis*. Jul 2014;14(7):590-599. Available at http://www.ncbi.nlm.nih.gov/pubmed/24908550.
10. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. Jul 2014;14(7):581-589. Available at http://www.ncbi.nlm.nih.gov/pubmed/24908551.
11. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect*

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Dis. Jul 2014;14(7):572-580. Available at http://www.ncbi.nlm.nih.gov/pubmed/24783988.

12. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. Jul 2015;15(7):785-792. Available at http://www.ncbi.nlm.nih.gov/pubmed/26062880.
13. Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. Jul 2015;15(7):775-784. Available at http://www.ncbi.nlm.nih.gov/pubmed/26062881.
14. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. Nov 29 2014;384(9958):1942-1951. Available at http://www.ncbi.nlm.nih.gov/pubmed/25103176.
15. van Lunzen J, Pozniak A, Gatell JM, et al. Brief Report: Switch to Ritonavir-Boosted Atazanavir Plus Raltegravir in Virologically Suppressed Patients With HIV-1 Infection: A Randomized Pilot Study. *J Acquir Immune Defic Syndr*. Apr 15 2016;71(5):538-543. Available at http://www.ncbi.nlm.nih.gov/pubmed/26605505.
16. Huhn G, Tebas P, Gallant J. Strategic simplification: The efficacy and safety of switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamde (E/C/F/TAF) plus darunavir (DRV) in treatment-experienced HIV-1 infected adults. Presented at: ID Week. 2015. San Diego, CA.
17. Figueroa MI, Sued O, Patterson P, Gun A, Rolon MJ, Cahn P. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naïve patients: First results of the PADDLE Trials. Presented at: 15th European AIDS Conference. 2015. Barcelona, Spain.
18. Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS*. Jan 28 2009;23(3):279-291. Available at http://www.ncbi.nlm.nih.gov/pubmed/19114854.
19. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. *HIV Med*. Aug 2012;13(7):398-405. Available at http://www.ncbi.nlm.nih.gov/pubmed/22413874.
20. Guiguet M, Ghosn J, Duvivier C, et al. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS*. Nov 28 2012;26(18):2345-2350. Available at http://www.ncbi.nlm.nih.gov/pubmed/22695301.
21. Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr*. Apr 1 2007;44(4):417-422. Available at http://www.ncbi.nlm.nih.gov/pubmed/17159658.
22. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS*. Sep 24 2010;24(15):2365-2374. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20802297.
23. Vernazza P, Daneel S, Schiffer V, et al. The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial. *AIDS*. Jun 19 2007;21(10):1309-1315. Available at http://www.ncbi.nlm.nih.gov/pubmed/17545707.
24. Bonjoch A, Pou C, Perez-Alvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. *J Antimicrob Chemother*. Jun 2013;68(6):1382-1387. Available at http://www.ncbi.nlm.nih.gov/pubmed/23354282.
25. Vitiello P, Brudney D, MacCartney M, et al. Responses to switching to maraviroc-based antiretroviral therapy in treated patients with suppressed plasma HIV-1-RNA load. *Intervirology*. 2012;55(2):172-178. Available at http://www.ncbi.nlm.nih.gov/pubmed/22286889.

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

Panel's Recommendations
• Therapeutic drug monitoring for antiretroviral agents is not recommended for routine use in the management of HIV-infected patients **(BII)**. • TDM may be considered in selected clinical scenarios, as discussed in the text below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

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

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

Several antiretroviral (ARV) agents meet most of the characteristics of agents suitable for a TDM strategy.[1] Specifically, some ARVs have considerable interpatient variability in drug concentrations; other ARVs have known drug concentrations associated with efficacy and/or toxicity; and in the case of other drugs, data from small prospective studies have demonstrated that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities.[2,3]

TDM for ARV agents, however, is not recommended for routine use in the management of HIV-infected adults (BII). This recommendation is based on multiple factors that limit the routine use of TDM in HIV-infected patients. These limiting factors include lack of prospective studies that demonstrate routine use of TDM improves clinical outcomes, uncertain therapeutic thresholds for most ARV agents, great intra- and inter-patient variability in drug concentrations achieved, and a lack of commercial laboratories to perform real time quantitation of ARV concentrations.[2-5]

Scenarios for Consideration of Therapeutic Drug Monitoring

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

- Suspect clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- Changes in pathophysiologic states that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- Among pregnant women who have risk factors for virologic failure (e.g., those not achieving viral suppression during earlier stage of pregnancy)—during the later stages of pregnancy, physiologic changes may result in reduced drug exposure and thus further increase the risk of virologic failure;

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- Heavily pretreated patients experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- Use of alternative dosing regimens and ARV combinations for which safety and efficacy have not been established in clinical trials;
- Concentration-dependent, drug-associated toxicities; and
- Lack of expected virologic response in medication-adherent patients.

Resources for Therapeutic Drug Monitoring Target Concentrations

Most TDM-proposed target concentrations for ARVs focus on a minimum concentration (C_{min}) (i.e., the plasma concentration at the end of a dosing interval before the next ARV dose). A summary of population average ARV C_{min} can be found in a review on the role of ARV-related TDM.[2] Population average C_{min} for newer ARVs can be found in the Food and Drug Administration-approved product labels.

Guidelines for the collection of blood samples and other practical suggestions related to TDM can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee.[4]

Challenges and Considerations in Using Drug Concentrations to Guide Therapy

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

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the drug concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

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

References

1. Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. *Clin Pharmacol Ther*. 1988;43(4):345-353. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3281773.
2. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. 2011;33(3):265-274. Available at http://www.ncbi.nlm.nih.gov/pubmed/21566505.
3. Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev*. 2009(3):CD007268. Available at http://www.ncbi.nlm.nih.gov/pubmed/19588422.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses*. 2002;18(12):825-834. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12201904.
5. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS*. 2008;3(3):266-271. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19372977.

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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 ARV 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 ARV 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

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(e.g., renal, cardiac, hepatic, or neurologic complications), development of drug resistance, and the need for chemoprophylaxis against opportunistic infections as a result of CD4 decline. Patients should be counseled about the need for close clinical and laboratory monitoring during therapy interruptions.

References

1. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med*. 2007;8(2):96-104. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17352766.
2. Kousignian I, Abgrall S, Grabar S, et al. Maintaining antiretroviral therapy reduces the risk of AIDS-defining events in patients with uncontrolled viral replication and profound immunodeficiency. *Clin Infect Dis*. 2008;46(2):296-304. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18171266.
3. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006;367(9527):1981-1989. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782488&itool=iconabstr&query_hl=147&itool=pubmed_docsum.
4. DART Trial Team DTT. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS*. 2008;22(2):237-247. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18097226.
5. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.

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Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early[a]) HIV Infection (Last updated January 28, 2016; last reviewed January 28, 2016)

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 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. Because resistance to pharmacokinetically enhanced protease inhibitors (PIs) emerges slowly and clinically significant transmitted resistance to PIs is uncommon, ritonavir-boosted darunavir (DRV/r) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is a recommended regimen in this setting **(AIII)**. For similar reasons, dolutegravir (DTG) plus TDF/FTC is also a reasonable option although data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of this regimen in early HIV infection is limited **(AIII)**.
- 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 treatment and should understand the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may recommend that patients defer therapy because of clinical and/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 is the phase of HIV-1 disease immediately after infection that is characterized by an initial burst of viremia; although anti-HIV-1 antibodies are undetectable, HIV-1 RNA or p24 antigen are present. Recent infection generally is considered the phase up to 6 months after infection during which anti-HIV-1 antibodies are detectable. Throughout this section, the term "early HIV-1 infection" is used to refer to either acute or recent HIV-1 infection.

An estimated 40% to 90% of patients with acute HIV-1 infection will experience symptoms of acute retroviral syndrome, such as fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms.[1-6] However, because the self-limiting symptoms are similar to those of many other viral infections, such as influenza and infectious mononucleosis, primary care clinicians often do not recognize acute HIV-1 infection. Acute infection can also be asymptomatic. Table 11 provides practitioners with guidance to recognize, diagnose, and manage acute HIV-1 infection.

Diagnosing Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV-1 infection in patients who have a compatible clinical syndrome—especially in those who report recent high-risk behavior (see Table 11).[7] Patients may not always disclose or admit to high-risk behaviors or perceive that their behaviors put them at risk for HIV-1 acquisition. Thus, even in the absence of reported high-risk behaviors, signs and symptoms consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

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.[7,8] Combination immunoassays that detect

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HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen are now approved by the Food and Drug Administration, and the most recent Centers for Disease Control and Prevention testing algorithm recommends them as the preferred assays to use for HIV screening, including for 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.[9] 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; a negative 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[9] (see Treatment for Early HIV-1 Infection). HIV-1 infection should be confirmed 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 very high (e.g., >100,000 copies/mL).[5,6] 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.[6] The diagnosis of HIV-1 infection should be confirmed by subsequent documentation of HIV antibody seroconversion (see Table 11).

Treating Early HIV-1 Infection

Clinical trial data regarding the treatment of early HIV-1 infection are limited. Many individuals who enrolled in studies to assess the role of ART in early HIV-1 infection were identified as trial participants because they presented with signs or symptoms of acute infection. With the introduction of HIV screening tests that include assays for HIV-1 RNA or p24 antigen and wider HIV screening in health care settings—particularly HIV testing associated with broader use of pre-exposure prophylaxis (PrEP) by individuals at higher risk for HIV—the number of asymptomatic patients identified with early infection may increase. The initial burst of high level viremia in infected individuals usually declines shortly after acute infection (e.g., within 2 months). However, there is a rationale for treatment during recent infection (e.g., 2–6 months after infection) because during the transition to chronic infection, the immune system may not yet have maximally contained viral replication in the lymphoid tissue.[10] Several trials have addressed the question of the long-term benefit of potent treatment regimens initiated during early HIV-1 infection. The potential benefits and risks of treating early HIV-1 infection are discussed below.

Potential Benefits of Treatment During Early HIV-1 Infection

Preliminary data indicate that treatment of early HIV-1 infection with ART improves laboratory markers of disease progression.[11-15] The data, though limited, indicate that treatment of early HIV-1 infection may also reduce the severity of acute disease, lower the viral set point,[16-18] reduce the size of the viral reservoir,[19] delay disease progression, enhance CD4 T lymphocyte (CD4) cell recovery,[20] and decrease the rate of viral mutation by suppressing viral replication and preserving immune function.[21] Because early HIV-1 infection is often associated with high viral loads and increased infectiousness,[22] and ART use by HIV-1-infected individuals reduces transmission to uninfected sexual partners,[23] treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission. In addition, although data are limited and the clinical relevance unclear, initiating ART during early HIV-1 infection may preserve mucosal Th17 cell function[24] and mitigate the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection.[25,26] Many of the potential benefits described above may be more likely to occur with treatment of acute infection, but they also may occur if treatment is initiated during recent HIV-1 infection.

The START Trial enrolled HIV-infected patients with CD4 counts >500 cells/mm^3 and randomized them to

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either start ART immediately or defer ART until their CD4 counts fell below 350 cells/mm^3 or an AIDS event occurred. The study demonstrated that immediate treatment resulted in a decrease in the combined endpoint of AIDS-defining illnesses, serious non-AIDS events, or death.[27] Similarly, TEMPRANO demonstrated decreased risk of death or severe HIV-related illness among HIV-infected patients who initiated ART with baseline CD4 counts >500 cells/mm^3.[28] The results from these studies strengthen the evidence for the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendation for ART initiation in all patients regardless of CD4 cell count **(AI)** (see Initiation of Antiretroviral Therapy section). Although neither trial collected specific information on patients with early infection, the strength of the overall results of the two studies and the evidence from 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 treatment. On a case-by-case basis, providers may recommend that patients defer therapy for clinical and/or psychosocial reasons. If treatment during early infection is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready.

Treating Early HIV-1 Infection During Pregnancy

Because early HIV-1 infection, especially in the setting of high level viremia, is associated with a high risk of perinatal transmission, all HIV-1-infected pregnant women should start ART as soon as possible to prevent perinatal transmission of HIV-1.[29]

Treatment Regimen for Early HIV-1 Infection

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients.[30,31] In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least 1 drug.[32] Therefore, before initiating ART in a person with early HIV-1 infection, genotypic antiretroviral (ARV) drug resistance testing should be performed to guide selection of an ARV regimen **(AII)**. However, treatment initiation should not be delayed pending resistance testing results. Once results are available, the treatment regimen can be modified if warranted **(AII)**.

As during chronic infection, the goal of therapy 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 therapy is started before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen should be used (darunavir/ritonavir [DRV/r] is recommended) because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon **(AIII)**. For similar reasons, dolutegravir (DTG) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is a reasonable treatment option, although data regarding transmission of INSTI-resistant HIV and the efficacy of DTG plus TDF/FTC in patients with acute/early infection are limited **(AIII)**. DTG/abacavir (ABC)/lamivudine (3TC) is not recommended for 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.

Given the increasing use of daily TDF/FTC for PrEP in HIV-negative individuals,[33-35] early infection may be diagnosed in some patients taking TDF/FTC for PrEP. In this setting, resistance testing should be performed; however, as described above, use of a pharmacologically boosted PI (DRV/r) and TDF/FTC or DTG and TDF/FTC remain reasonable treatment options pending resistance testing results (see What to Start).

Patient Follow-Up

Testing for plasma HIV-1 RNA levels, CD4 cell counts, and toxicity monitoring should be performed as

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described in Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy (e.g., HIV-1 RNA at initiation of therapy, after 2 to 8 weeks, 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 as in guidelines for patients with chronic infection. Recent studies of early HIV-1 infection have shown some benefits of starting and then stopping treatment as a potential therapeutic strategy.[16-18] However, a large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful in terms of increased risk of AIDS and non-AIDS events,[36] and that the strategy was associated with increased markers of inflammation, immune activation, and coagulation.[37] For these reasons and the potential benefit of ART in reducing the risk of HIV-1 transmission, the Panel recommends indefinite continuation of ART in patients treated for early HIV-1 infection **(AIII)**.

Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Acute HIV-1 infection should be considered in individuals with signs or symptoms 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, transaminase elevation.
- High-risk exposures include sexual contact with an HIV-1-infected person 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 potentially infected with HIV.
- **Differential diagnosis:** The differential diagnosis of patients presenting with HIV-1 infection may include but is not limited to viral illnesses such as Epstein-Barr virus (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 antigen/antibody [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.

ART After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all HIV-infected individuals **(AI)**, and should be offered to all patients with early HIV-1 infection.
- All pregnant women with early HIV-1 infection should begin ART as soon as possible for their health and to prevent perinatal transmission of HIV-1.
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**.
- If ART is initiated before drug resistance test results are available, a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. DRV/r plus TDF/FTC is a recommended regimen in this setting **(AIII)**. For similar reasons, DTG plus TDF/FTC is a reasonable option although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited **(AIII)**.
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted **(AII)**. In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens that is 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; 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.

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Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; DRV/r = darunavir/ritonavir; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TDF/FTC = tenofovir disoproxil fumerate/emtricitabine

References

1. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. *AIDS*. Jan 1991;5(1):1-14. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1812848.
2. Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis*. Dec 1993;168(6):1490-1501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8245534.
3. Kinloch-de Loes S, de Saussure P, Saurat JH, Stalder H, Hirschel B, Perrin LH. Symptomatic primary infection due to human immunodeficiency virus type 1: review of 31 cases. *Clin Infect Dis*. Jul 1993;17(1):59-65. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8353247.
4. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. Aug 15 1996;125(4):257-264. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8678387.
5. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med*. Jan 2 2001;134(1):25-29. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11187417.
6. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. May 24 2002;16(8):1119-1129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12004270.
7. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16988643.
8. Pilcher CD, Christopoulos KA, Golden M. Public health rationale for rapid nucleic acid or p24 antigen tests for HIV. *J Infect Dis*. Apr 15 2010;201 Suppl 1:S7-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/20225950.
9. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. 2014. Available at http://stacks.cdc.gov/view/cdc/23447. Accessed January 12, 2016.
10. Pantaleo G, Cohen OJ, Schacker T, et al. Evolutionary pattern of human immunodeficiency virus (HIV) replication and distribution in lymph nodes following primary infection: implications for antiviral therapy. *Nat Med*. Mar 1998;4(3):341-345. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9500610.
11. Hoen B, Dumon B, Harzic M, et al. Highly active antiretroviral treatment initiated early in the course of symptomatic primary HIV-1 infection: results of the ANRS 053 trial. *J Infect Dis*. Oct 1999;180(4):1342-1346. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10479169.
12. Lafeuillade A, Poggi C, Tamalet C, Profizi N, Tourres C, Costes O. Effects of a combination of zidovudine, didanosine, and lamivudine on primary human immunodeficiency virus type 1 infection. *J Infect Dis*. May 1997;175(5):1051-1055. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9129065.
13. Lillo FB, Ciuffreda D, Veglia F, et al. Viral load and burden modification following early antiretroviral therapy of primary HIV-1 infection. *AIDS*. May 7 1999;13(7):791-796. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10357377.
14. Malhotra U, Berrey MM, Huang Y, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. *J Infect Dis*. Jan 2000;181(1):121-131. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10608758.
15. Smith DE, Walker BD, Cooper DA, Rosenberg ES, Kaldor JM. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS*. Mar 26 2004;18(5):709-718. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15075505.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

16. Hogan CM, Degruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J Infect Dis*. Jan 1 2012;205(1):87-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/22180621.
17. Grijsen ML, Steingrover R, Wit FW, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. *PLoS Med*. 2012;9(3):e1001196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22479156.
18. Hamlyn E, Ewings FM, Porter K, et al. Plasma HIV viral rebound following protocol-indicated cessation of ART commenced in primary and chronic HIV infection. *PLoS One*. 2012;7(8):e43754. Available at http://www.ncbi.nlm.nih.gov/pubmed/22952756.
19. Strain MC, Little SJ, Daar ES, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. *J Infect Dis*. May 1 2005;191(9):1410-1418. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809898.
20. SPARTAC Trial Investigators, Fidler S, Porter K, et al. Short-course antiretroviral therapy in primary HIV infection. *N Engl J Med*. Jan 17 2013;368(3):207-217. Available at http://www.ncbi.nlm.nih.gov/pubmed/23323897.
21. Rosenberg ES, Altfeld M, Poon SH, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature*. Sep 28 2000;407(6803):523-526. Available at http://www.ncbi.nlm.nih.gov/pubmed/11029005.
22. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis*. May 1 2005;191(9):1403-1409. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809897.
23. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21767103.
24. Schuetz A, Deleage C, Sereti I, et al. Initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverses HIV-related immune activation. *PLoS Pathog*. Dec 2014;10(12):e1004543. Available at http://www.ncbi.nlm.nih.gov/pubmed/25503054.
25. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med*. Sep 20 2004;200(6):761-770. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15365095.
26. Guadalupe M, Reay E, Sankaran S, et al. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol*. Nov 2003;77(21):11708-11717. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14557656.
27. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. Jul 20 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.
28. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and Isoniazid preventive therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.
29. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014. Available at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. Accessed March 19, 2015.
30. Kim D, Ziebell R, Saduvala N, et al. Trend in transmitted HIV-1 ARV drug Resistance-associated mutations: 10 HIV surveillance areas, U.S., 2007–2010. Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, Georgia.
31. Hofstra LM, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. *Clin Infect Dis*. Nov 29 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/26620652.
32. Yanik EL, Napravnik S, Hurt CB, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. *J Acquir Immune Defic Syndr*. Oct 1 2012;61(2):258-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/22692092.
33. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. Dec 30 2010;363(27):2587-2599. Available at http://www.ncbi.nlm.nih.gov/pubmed/21091279.
34. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. Aug 2 2012;367(5):399-410. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784037.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

35. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. Aug 2 2012;367(5):423-434. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784038.
36. Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren J, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. Nov 30 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/pubmed/17135583.
37. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. Oct 21 2008;5(10):e203. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18942885.

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HIV-Infected Adolescents and Young Adults (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Summary and Panel's Recommendations
• HIV-infected adolescents 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 HIV-infected individuals **(AI)** to reduce morbidity and mortality. Thus, ART is also recommended for ART-naive adolescents. However, 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 success in achieving sustained viral suppression **(AII)**. • The adolescent sexual maturity rating can be helpful to guide regimen selection for initiation of or changes in ART as recommended by either these Adult and Adolescent ART Guidelines or the Pediatric ART Guidelines. These Adult/Adolescent Guidelines are more appropriate for postpubertal adolescents (i.e., sexual maturity rating IV or V) **(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 insure 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 HIV-infected children 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 new HIV infections diagnosed in 2010 were among youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% among young gay and bisexual men who have sex with men (MSM).[1] Among youth living with HIV infection in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they were HIV-infected.[2] Trends in HIV/AIDS prevalence indicate that the disproportionate burden of AIDS among racial minorities is even greater among minority youth 13 to 24 years of age (64% to 66% of cases) than among those older than 24 years (48% of cases).[3] 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. HIV-infected adolescents represent a heterogeneous group in terms of socio-demographics, mode of HIV infection, 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 are infected through sex. Many of them are recently infected and unaware of their HIV infection status. Thus, 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.[4] High grade viremia was reported in a cohort of youth identified as HIV-infected 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.[5] A study among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.[6] Substantial multiclass resistance was noted in a cohort of non-perinatally infected, treatment-naive youth

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who were screened for an ARV treatment trial.[7] As these youth were naive to all ART, this reflects transmission of resistant virus. This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and may be more ART experienced; thus, using baseline resistance testing to guide initial therapy in recently infected youth naive to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection 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 infected later in life.[8] Adolescents infected 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 section).

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and 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 challenges with youth remaining in care and achieving long-term viral suppression,[9] additional considerations may be given to more intensive case management approaches.[10,11] Adolescents may seek care in several settings including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.[12] Where youth services are available, they may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents.[13] Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.[12,14]

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 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 similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of HIV-infected American youth, 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 success in achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR) (also known as Tanner stage) can be helpful when ART initiation is being considered for this population (see SMR table). Adult guidelines for ART initiation or regimen changes (see Adult Guidelines, What to Start) are usually appropriate for postpubertal adolescents (SMR IV or V) because the clinical course of HIV infection in postpubertal adolescents who were infected 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 were perinatally infected and whose long-term HIV infection has not affected their sexual maturity (SMR IV or V). Pediatric guidelines for ART may be more appropriate for adolescents infected with HIV during their teen years (e.g., through sex), but who are sexually immature (SMR III or less) and for perinatally infected adolescents with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other co-morbidities (SMR III or less) (see What to Start in the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).

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Perinatally infected, postpubertal youth 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 Recovery, Regimen Switching in the Setting of Virologic Suppression, and Adverse Effects of Antiretroviral Agents). Perinatally infected postpubertal adolescents may also have comorbid cognitive impairments that compound adherence challenges common among youth.[15]

Dosage of ARV drugs should be prescribed according to the SMR and not solely on the basis of age.[16,17] Adolescents in early puberty (i.e., SMR I-III) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., SMR IV-V) should follow adult dosing schedules. However, SMR stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children who were infected with HIV perinatally,[18] 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., Tanner Stage III in females and Tanner Stage IV in males) 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 selected circumstances to help guide therapy decisions. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.[19]

Adherence Concerns in Adolescents

HIV-infected adolescents are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who frequently lack both health insurance and experience with health care systems. Studies in adolescents infected in their teen years and in adolescents infected through perinatal transmission demonstrate that many adolescents in both groups face numerous barriers to adherence.[20-22] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[23] Reasons that HIV-infected adolescents often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV infection;
- 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 infection if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, beepers, timers, and pill boxes) that are stylish and/or inconspicuous.[24] In a randomized controlled study among non-adherent youth 15 to 24 years of age, youth who

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received cell phone medication reminders demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls.[25] It is important to make medication adherence as user friendly and the least stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take 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.[26-28] Directly observed therapy may be considered for some HIV-infected adolescents such as those with mental illness.[29-33]

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. The ability of youth to adhere to therapy needs to be considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth who, although needing therapy, 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 treatment 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 genetic resistance barriers.

Such decisions are ideally individualized to each patient and should be made carefully in context with the individual's clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see the Adherence to ART section of these guidelines and the Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.[19]

Special Considerations in Adolescents

All adolescents should be screened for sexually transmitted diseases (STDs), in particular human papilloma virus (HPV). In young MSM, screening for STDs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.[34] For a more detailed discussion on STDs, see the most recent CDC guidelines[35] and the adult and pediatric opportunistic infection treatment and prevention guidelines on HPV among HIV-infected adolescents.[36,37] Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for HIV-infected female adolescents is especially important. Contraception, including the interaction of specific ARV drugs with hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see HIV-Infected Women and the Perinatal Guidelines.[38] Finally, HIV-infected transgender youth represent an important population that requires additional psychosocial and healthcare considerations. For a more detailed discussion, see Adolescent Trials Network (ATN) 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 HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some

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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 referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as 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, HIV-infected adolescents belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial considerations and needs:

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

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on.[39] 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 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 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 and before the actual transition process.[40] Attention to the key interventions noted above will likely improve adherence to appointments and avert the potential for a youth to fall through the cracks, as it is commonly referred to in adolescent medicine. For a more detailed discussion on specific topics on transitioning care for adolescents and young adults, see http://www.hivguidelines.org/clinical-guidelines/adolescents/transitioning-hiv-infected-adolescents-into-adult-care/.

References

1. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2010. *HIV Surveillance Supplemental Report 2012;17(No. 3, part A)*. Table 5a. 2012. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed January

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

6, 2015.

2. Centers for Disease C, Prevention. Vital signs: HIV infection, testing, and risk behaviors among youths—United States. *MMWR Morb Mortal Wkly Rep*. Nov 30 2012;61(47):971-976. Available at http://www.ncbi.nlm.nih.gov/pubmed/23190571.
3. Centers for Disease Control and Prevention. HIV Surveillance in Adolescents and Young Adults. 2011. Available at http://www.cdc.gov/hiv/pdf/statistics_surveillance_Adolescents.pdf. Accessed January 15, 2016.
4. Philbin MM, Tanner AE, Duval A, Ellen J, Kapogiannis B, Fortenberry JD. Linking HIV-positive adolescents to care in 15 different clinics across the United States: Creating solutions to address structural barriers for linkage to care. *AIDS Care*. Jan 2014;26(1):12-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/23777542.
5. Ellen JM, Kapogiannis B, Fortenberry JD, et al. HIV viral load levels and CD4+ cell counts of youth in 14 cities. *AIDS*. May 15 2014;28(8):1213-1219. Available at http://www.ncbi.nlm.nih.gov/pubmed/25028912.
6. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis*. Dec 1 2006;194(11):1505-1509. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17083034.
7. Agwu AL, Bethel J, Hightow-Weidman LB, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. *AIDS Patient Care STDS*. Apr 2012;26(4):193-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/22563607.
8. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. Jun 1 2011;57(2):165-173. Available at http://www.ncbi.nlm.nih.gov/pubmed/21407086.
9. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. *AIDS Patient Care STDS*. Mar 2014;28(3):128-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/24601734.
10. Hightow-Weidman LB, Smith JC, Valera E, Matthews DD, Lyons P. Keeping them in "STYLE": finding, linking, and retaining young HIV-positive black and Latino men who have sex with men in care. *AIDS Patient Care STDS*. Jan 2011;25(1):37-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/21162690.
11. Sitapati AM, Limneos J, Bonet-Vazquez M, Mar-Tang M, Qin H, Mathews WC. Retention: building a patient-centered medical home in HIV primary care through PUFF (Patients Unable to Follow-up Found). *J Health Care Poor Underserved*. Aug 2012;23(3 Suppl):81-95. Available at http://www.ncbi.nlm.nih.gov/pubmed/22864489.
12. Tanner AE, Philbin MM, Duval A, et al. "Youth friendly" clinics: Considerations for linking and engaging HIV-infected adolescents into care. *AIDS Care*. Feb 2014;26(2):199-205. Available at http://www.ncbi.nlm.nih.gov/pubmed/23782040.
13. Davila JA, Miertschin N, Sansgiry S, Schwarzwald H, Henley C, Giordano TP. Centralization of HIV services in HIV-positive African-American and Hispanic youth improves retention in care. *AIDS Care*. 2013;25(2):202-206. Available at http://www.ncbi.nlm.nih.gov/pubmed/22708510.
14. New York State Department of Health AIDS Institute. *Ambulatory Care of HIV-Infected Adolescents*. 2012. Available at http://hivguidelines.org/wp-content/uploads/2012/11/ambulatory-care-of-hiv-infected-adolescents-11-19-2012.pdf. Accessed January 6, 2016.
15. Nichols SL, Brummel SS, Smith RA, et al. Executive Functioning in Children and Adolescents With Perinatal HIV Infection. *Pediatr Infect Dis J*. Sep 2015;34(9):969-975. Available at http://www.ncbi.nlm.nih.gov/pubmed/26376309.
16. Rogers A (ed). Pharmacokinetics and pharmacodynamics in adolescents. *J Adolesc Health*. 1994;15:605-678.
17. El-Sadar W, Oleske JM, Agins BD, et al. Evaluation and management of early HIV infection. Clinical Practice Guideline No. 7 (AHCPR Publication No. 94-0572). Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services. 1994.
18. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr*. 2003;33(1):56-65. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12792356&query_hl=17&itool=pubmed_docsum.
19. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection*. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed January 15, 2016.

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20. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. *AIDS Patient Care STDS*. Feb 2010;24(2):97-104. Available at http://www.ncbi.nlm.nih.gov/pubmed/20059354.
21. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. Mar 2009;23(3):185-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/19866536.
22. MacDonell K, Naar-King S, Huszti H, Belzer M. Barriers to medication adherence in behaviorally and perinatally infected youth living with HIV. *AIDS Behav*. Jan 2013;17(1):86-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/23142855.
23. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr*. Oct 1 2011;58(2):193-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/21826014.
24. Lyon ME, Trexler C, Akpan-Townsend C, et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. *AIDS Patient Care STDS*. Jun 2003;17(6):299-308. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12880493.
25. Belzer ME, Kolmodin MacDonell K, Clark LF, et al. Acceptability and Feasibility of a Cell Phone Support Intervention for Youth Living with HIV with Nonadherence to Antiretroviral Therapy. *AIDS Patient Care STDS*. Jun 2015;29(6):338-345. Available at http://www.ncbi.nlm.nih.gov/pubmed/25928772.
26. Brooks-Gunn J, Graber JA. Puberty as a biological and social event: implications for research on pharmacology. *J Adolesc Health*. Dec 1994;15(8):663-671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7696287.
27. Kyngas H, Hentinen M, Barlow JH. Adolescents' perceptions of physicians, nurses, parents and friends: help or hindrance in compliance with diabetes self-care? *J Adv Nurs*. Apr 1998;27(4):760-769. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9578206.
28. La Greca AM. Peer influences in pediatric chronic illness: an update. *J Pediatr Psychol*. Dec 1992;17(6):775-784. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1484338.
29. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care*. Feb 2001;13(1):27-40. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11177463.
30. Stenzel MS, McKenzie M, Mitty JA, Flanigan TP. Enhancing adherence to HAART: a pilot program of modified directly observed therapy. *AIDS Read*. Jun 2001;11(6):317-319, 324-328. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11449925.
31. Purdy JB, Freeman AF, Martin SC, et al. Virologic response using directly observed therapy in adolescents with HIV: an adherence tool. *J Assoc Nurses AIDS Care*. Mar-Apr 2008;19(2):158-165. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18328966.
32. Garvie PA, Lawford J, Flynn PM, et al. Development of a directly observed therapy adherence intervention for adolescents with human immunodeficiency virus-1: application of focus group methodology to inform design, feasibility, and acceptability. *J Adolesc Health*. Feb 2009;44(2):124-132. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19167660.
33. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses*. Sep 2010;26(9):947-953. Available at http://www.ncbi.nlm.nih.gov/pubmed/20707731.
34. Vermund SH, Wilson CM, Rogers AS, Partlow C, Moscicki AB. Sexually transmitted infections among HIV infected and HIV uninfected high-risk youth in the REACH study. Reaching for Excellence in Adolescent Care and Health. *J Adolesc Health*. Sep 2001;29(3 Suppl):49-56. Available at http://www.ncbi.nlm.nih.gov/pubmed/11530303.
35. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21160459.
36. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease

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Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed January 15, 2016.

37. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed January 15, 2016.
38. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed January 15, 2016.
39. Valenzuela JM, Buchanan CL, Radcliffe J, et al. Transition to adult services among behaviorally infected adolescents with HIV--a qualitative study. *J Pediatr Psychol*. Mar 2011;36(2):134-140. Available at http://www.ncbi.nlm.nih.gov/pubmed/19542198.
40. Committee On Pediatric A. Transitioning HIV-infected youth into adult health care. *Pediatrics*. Jul 2013;132(1):192-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/23796739.

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HIV and Illicit Drug Users (Last updated March 27, 2012; last reviewed March 27, 2012)

Treatment Challenges of HIV-Infected Illicit Drug Users

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

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

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

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

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although illicit drug users are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in illicit drug users—when they are not actively using drugs—is similar to that seen in other

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populations.[10] Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se.[11] Providers need to remain attentive to the possible impact of disruptions caused by drug use on the patient both before and while receiving ART. Although many illicit drug users can sufficiently control their drug use for long enough time to benefit from care, substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating, flexible, community-based HIV care sites that are characterized by familiarity with and nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence.[9] These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise in this population.[12]

Antiretroviral Agents and Opioid Substitution Therapy

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

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

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

Naltrexone and Antiretroviral Therapy. A once-monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[15]

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

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

Summary

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

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

References

1. Colfax G, Guzman R. Club drugs and HIV infection: a review. *Clin Infect Dis*. May 15 2006;42(10):1463-1469.
2. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med*. May 2003;114(7):573-580.
3. Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr*. Apr 15 2006;41(5):563-572.
4. Wang C, Vlahov D, Galai N, et al. The effect of HIV infection on overdose mortality. *AIDS*. Jun 10 2005;19(9):935-942.
5. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. *JAMA*. Aug 12 1998;280(6):547-549.
6. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported antiretroviral therapy in injection drug users. *JAMA*. Aug 12 1998;280(6):544-546.
7. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr*. Sep 1 2001;28(1):47-58.
8. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *Lancet*. Jul 31 2010;376(9738):367-387.
9. Bruce RD, Altice FL, Friedland GH, Volberding P. HIV Disease Among Substance Misusers: Treatment Issues. *Global AIDS/HIV Medicine*. San Diego, CA: Elsevier Inc; 2007:513-526.
10. Morris JD, Golub ET, Mehta SH, Jacobson LP, Gange SJ. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. *AIDS Res Ther*. 2007;4:12.

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11. Bouhnik AD, Chesney M, Carrieri P, et al. Nonadherence among HIV-infected injecting drug users: the impact of social instability. *J Acquir Immune Defic Syndr*. Dec 15 2002;31(Suppl 3):S149-153.
12. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis*. Sep 15 2007;45(6):770-778.
13. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep*. Aug 2010;7(3):152-160.
14. Bruce RD, McCance-Katz E, Kharasch ED, Moody DE, Morse GD. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. *Clin Infect Dis*. Dec 15 2006;43(Suppl 4):S216-223.
15. Food and Drug Administration (FDA). Vivitrol (package insert). October 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf.
16. Bruce RD, Altice FL, Gourevitch MN, Friedland GH. A review of pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: Implications and management for clinical practice. *Exp Rev of Clin Pharmacol*. 2008;1(1):115-127.
17. Hicks PL, Mulvey KP, Chander G, et al. The impact of illicit drug use and substance abuse treatment on adherence to HAART. *AIDS Care*. Oct 2007;19(9):1134-1140.
18. Cofrancesco J, Jr., Scherzer R, Tien PC, et al. Illicit drug use and HIV treatment outcomes in a US cohort. *AIDS*. Jan 30 2008;22(3):357-365.

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HIV-Infected Women (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all HIV-infected women to improve their health and to reduce the risk of HIV transmission to HIV-uninfected sex partners **(AI)**. • In pregnant women, an additional goal of therapy 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 antiretroviral (ARV) combination regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and pharmacokinetic (PK) data on use during pregnancy for each agent. The risks and benefits of ARV use during pregnancy should be discussed with all women **(AIII)**. • For women taking ARV drugs that have significant PK interactions with hormonal contraceptives, an alternative or additional effective contraceptive method to prevent unintended pregnancy is recommended **(AIII)**. Switching to an ARV drug without interactions with hormonal contraceptives may also be considered **(BIII)**. • Nonpregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (EFV) and receive counseling about the potential risk to the fetus and desirability of avoiding conception while on EFV-based regimens **(AIII)**. • When designing a regimen for a pregnant woman, clinicians should consult the most current Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) **(AIII)**. • Regimens that do not include EFV should be considered in women who are planning to become pregnant or are sexually active and not using effective contraception **(BIII)**. • Women on a suppressive regimen containing EFV who become pregnant and present to antenatal care during the first trimester can continue EFV throughout pregnancy **(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*

This section discusses some unique issues to consider and basic principles to follow when caring for HIV-infected women, including during pregnancy. Clinicians who care for pregnant women should consult the current Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) for a more in-depth discussion and guidance on managing these patients.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown gender differences in virologic responses to antitretroviral therapy (ART).[1-4] However, there are limited data showing that pharmacokinetics (PKs) for some antiretroviral (ARV) drugs may differ between men and women, possibly because of variations between men and women 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 have suggested that gender 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 (d4T), and didanosine (ddI).[10] These agents are no longer recommended for use in HIV-infected patients in the United States; although ZDV is still administered intravenously to women during delivery, it is not generally recommended for long-term use.

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Some studies have compared women and men in relation to metabolic complications associated with ARV use. Over 96 weeks following initiation of ART, HIV-infected women are less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than HIV-infected men.[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 (RAL).[17-20] Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF; a new oral tenofovir prodrug that induces less bone loss than TDF) may be considered as alternatives to TDF in patients who are at risk of osteopenia or osteoporosis. Recommendations for management of bone disease in HIV-infected patients have been published.[21]

HIV-Infected Women of Childbearing Potential

All HIV-infected women 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 unintended 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 Perinatal Guidelines).

Reproductive Options for Serodiscordant Couples

HIV infected and uninfected women who wish to conceive with an HIV-uninfected or infected male partner (respectively) 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), ART to maximally suppress and maintain the infected partner's viral load, use of pre-exposure prophylaxis by the uninfected partner,[22-24] male circumcision, and/or self-insemination with the HIV-uninfected partner's sperm during the HIV-infected woman's periovulatory period.[25]

Efavirenz (EFV) is teratogenic in nonhuman primates. Nonpregnant women of childbearing potential should have a pregnancy test before starting EFV and be advised of potential EFV-related risks to the fetus and the desirability of avoiding conception while on an EFV-based regimen **(AIII)**. Regimens that do not include EFV should be considered in women who are planning to become pregnant or who are sexually active and not using effective contraception **(BIII)**. The most vulnerable period in fetal organogenesis is early in gestation, usually before pregnancy is recognized. Efavirenz use after the first 8 weeks of pregnancy appears safe.

Hormonal Contraception

Safe and effective reproductive health and family planning services to prevent unintended pregnancies and perinatal transmission of HIV are an essential component of care for HIV-infected women of childbearing age. These women should receive ongoing counseling on reproductive issues. Regardless of hormonal contraceptive use, HIV-infected women should be advised to consistently use condoms (male or female) during sex and adhere to an HIV regimen effective in maintaining viral suppression. Both strategies are crucial to prevent transmission of HIV to uninfected partners and to protect against infection with other STIs. The following are some considerations 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 levels that may reduce contraceptive efficacy or increase adverse effects are unknown.

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- **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 19a, 19b, and 19d), which potentially decreases contraceptive efficacy or increases 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.[26] Several PI/r and EVG/c decrease oral contraceptive estradiol levels.[27-30] Several PK studies have shown that ETR, RPV, and NVP use did not significantly affect estradiol or progestin levels in HIV-infected women using COCs.[31-33]
- **Injectable Contraceptives:** Small studies of HIV-infected women 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.[34-37]
- **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.[38,39] Two studies identified lower exposure of levonorgestrel and etonogestrel released from an implant when combined with EFV-based ART.[40,41] These PK studies did not identify any change in hormone concentrations when the implants were used in women taking NVP[40] or LPV/r.[41] 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.[42,43]

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women 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 ARVs (see drug interaction Tables 19a, 19b, and 19d and 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.[44] Most of the retrospective studies were done in the setting where the HIV-infected partners were not taking ART. A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the HIV-infected partner was not receiving ART found that women using hormonal contraception (the majority using injectable DMPA) had a twofold increased risk of acquiring or transmitting HIV. HIV-infected women using hormonal contraception had higher genital HIV RNA concentrations than those not using hormonal contraceptives.[45] 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 and HIV transmission to an uninfected partner and recommended that women living with HIV can continue to use all existing hormonal contraceptive methods without restriction.[46] Further research is needed to definitively determine if 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 HIV-infected women.[47-49] Although studies have focused primarily on non-hormone-containing IUDs (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.[50-52]

Pregnant Women

Clinicians caring for HIV-infected pregnant women should review the Perinatal Guidelines. The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic,

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immunologic, or clinical parameters, for their own health and to prevent transmission of HIV to the fetus **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits and risks of ARV use during pregnancy to the woman, fetus, and newborn. Women should be counseled and strongly encouraged to receive ART for their own health and that of their infants. Open, non-judgmental and supportive discussion should be used to encourage women to adhere to care.

Prevention of Perinatal Transmission of HIV

The use of ART and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV.[53-55] The goal of ART is to achieve maximal and sustained viral suppression throughout pregnancy. Long-term follow-up is recommended for all infants born to women who receive ART during pregnancy, regardless of the infant's HIV status (see the Perinatal Guidelines).

ARV Regimen Considerations

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

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

ART is considered the standard of care for HIV-infected pregnant women, both to treat HIV infection and prevent perinatal transmission of HIV. If a pregnant woman receiving an EFV-based regimen presents to prenatal care during the first trimester with suppressed HIV RNA, EFV can be continued. This is because the risk of fetal neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy. Unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission. Detailed recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines.

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

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (http://www.apregistry.com). The registry collects observational data regarding exposure to Food and Drug Administration (FDA)-approved ARV drugs during pregnancy to assess potential teratogenicity. Analysis of the Antiretroviral Pregnancy Registry data indicates that there is no clear association between first-trimester exposure to any ARV drug and increased risk of birth defects. For more information regarding selection and use of ART during pregnancy, refer to the Perinatal Guidelines.

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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, women should be counseled to avoid breastfeeding.[56] HIV-infected women should not premasticate food and feed it to their infants because the practice has been associated with mother-to-child transmission of HIV.[57] ART is currently recommended for all HIV-infected individuals **(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.[58-60] Clinicians caring for postpartum women who are receiving ART should address adherence, including an evaluation of specific facilitators and barriers to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to Antiretroviral Therapy).

References

1. Collazos J, Asensi V, Carton JA. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. *AIDS*. Apr 23 2007;21(7):835-843. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17415038.
2. Fardet L, Mary-Krause M, Heard I, Partisani M, Costagliola D. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. *HIV Med*. Nov 2006;7(8):520-529. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17105511.
3. Currier J, Averitt Bridge D, Hagins D, et al. Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial. *Ann Intern Med*. Sep 21 2010;153(6):349-357. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20855799.
4. Rosin C, Elzi L, Thurnheer C, et al. Gender inequalities in the response to combination antiretroviral therapy over time: the Swiss HIV Cohort Study. *HIV Med*. May 2015;16(5):319-325. Available at http://www.ncbi.nlm.nih.gov/pubmed/25329751.
5. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol*. 2004;44:499-523. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14744256.
6. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: a review of sex differences. *Gend Med*. Jun 2007;4(2):106-119. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17707845.
7. Venuto CS, Mollan K, Ma Q, et al. Sex differences in atazanavir pharmacokinetics and associations with time to clinical events: AIDS Clinical Trials Group Study A5202. *J Antimicrob Chemother*. Dec 2014;69(12):3300-3310. Available at http://www.ncbi.nlm.nih.gov/pubmed/25159623.
8. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15021321.
9. Wit FW, Kesselring AM, Gras L, et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis*. Mar 15 2008;46(6):933-940. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18271750.
10. Lactic Acidosis International Study Group LAISG. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS*. Nov 30 2007;21(18):2455-2464. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18025882.
11. McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis*. Jul 15 2011;53(2):185-196. Available at http://www.ncbi.nlm.nih.gov/pubmed/21690627.

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12. Galli M, Veglia F, Angarano G, et al. Gender differences in antiretroviral drug-related adipose tissue alterations. Women are at higher risk than men and develop particular lipodystrophy patterns. *J Acquir Immune Defic Syndr*. Sep 1 2003;34(1):58-61. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14501794.
13. Yin M, Dobkin J, Brudney K, et al. Bone mass and mineral metabolism in HIV+ postmenopausal women. *Osteoporos Int*. Nov 2005;16(11):1345-1352. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15754081.
14. Brown TT, Qaqish RB. Response to Berg et al. 'Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review'. *AIDS*. Aug 20 2007;21(13):1830-1831. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17690589.
15. Sharma A, Shi Q, Hoover DR, et al. Increased Fracture Incidence in Middle-Aged HIV-Infected and HIV-Uninfected Women: Updated Results From the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr*. Sep 1 2015;70(1):54-61. Available at http://www.ncbi.nlm.nih.gov/pubmed/26322667.
16. Grant PM, Kitch D, McComsey GA, et al. Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. *Clin Infect Dis*. Nov 2013;57(10):1483-1488. Available at http://www.ncbi.nlm.nih.gov/pubmed/23943825.
17. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. Oct 15 2010;51(8):963-972. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20828304.
18. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis*. Nov 15 2009;49(10):1591-1601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19842973.
19. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. *AIDS*. Apr 27 2009;23(7):817-824. Available at http://www.ncbi.nlm.nih.gov/pubmed/19363330.
20. Brown TT, Moser C, Currier JS, et al. Changes in Bone Mineral Density After Initiation of Antiretroviral Treatment With Tenofovir Disoproxil Fumarate/Emtricitabine Plus Atazanavir/Ritonavir, Darunavir/Ritonavir, or Raltegravir. *J Infect Dis*. Oct 15 2015;212(8):1241-1249. Available at http://www.ncbi.nlm.nih.gov/pubmed/25948863.
21. Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis*. Apr 15 2015;60(8):1242-1251. Available at http://www.ncbi.nlm.nih.gov/pubmed/25609682.
22. Heffron R, Pintye J, Matthews LT, Weber S, Mugo N. PrEP as Peri-conception HIV Prevention for Women and Men. *Curr HIV/AIDS Rep*. Mar 18 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26993627.
23. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. *AIDS*. Oct 23 2011;25(16):2005-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21716070.
24. Whetham J, Taylor S, Charlwood L, et al. Pre-exposure prophylaxis for conception (PrEP-C) as a risk reduction strategy in HIV-positive men and HIV-negative women in the UK. *AIDS Care*. 2014;26(3):332-336. Available at http://www.ncbi.nlm.nih.gov/pubmed/23876052.
25. Lampe MA, Smith DK, Anderson GJ, Edwards AE, Nesheim SR. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States. *Am J Obstet Gynecol*. Jun 2011;204(6):488 e481-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/21457911.
26. Sevinsky H, Eley T, Persson A, et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther*. 2011;16(2):149-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/21447863.
27. Vogler MA, Patterson K, Kamemoto L, et al. Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188. *J Acquir Immune Defic Syndr*. Dec 2010;55(4):473-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/20842042.
28. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. *Antivir Ther*. 2011;16(2):157-164. Available at http://www.ncbi.nlm.nih.gov/pubmed/21447864.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

29. Food and Drug Administration. Stribild (package insert). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf. Accessed May 16, 2016. 2016.
30. Food and Drug Administration. Genvoya (package insert). Gilead. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207561s000lbl.pdf. Last accessed May 16, 2016.
31. Scholler-Gyure M, Kakuda TN, Woodfall B, et al. Effect of steady-state etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and norethindrone. *Contraception*. Jul 2009;80(1):44-52. Available at http://www.ncbi.nlm.nih.gov/pubmed/19501215.
32. Crauwels HM, van Heeswijk RP, Buelens A, Stevens M, Hoetelmans RM. Lack of an effect of rilpivirine on the pharmacokinetics of ethinylestradiol and norethindrone in healthy volunteers. *Int J Clin Pharmacol Ther*. Feb 2014;52(2):118-128. Available at http://www.ncbi.nlm.nih.gov/pubmed/24161160.
33. Stuart GS, Moses A, Corbett A, et al. Combined oral contraceptives and antiretroviral PK/PD in Malawian women: pharmacokinetics and pharmacodynamics of a combined oral contraceptive and a generic combined formulation antiretroviral in Malawi. *J Acquir Immune Defic Syndr*. Oct 1 2011;58(2):e40-43. Available at http://www.ncbi.nlm.nih.gov/pubmed/21921726.
34. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. Feb 2007;81(2):222-227. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17192768.
35. Nanda K, Amaral E, Hays M, Viscola MA, Mehta N, Bahamondes L. Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy. *Fertil Steril*. Oct 2008;90(4):965-971. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17880953.
36. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. Feb 2008;77(2):84-90. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18226670.
37. Luque AE, Cohn SE, Park JG, et al. Depot medroxyprogesterone acetate in combination with a twice-daily lopinavir-ritonavir-based regimen in HIV-infected women showed effective contraception and a lack of clinically significant interactions, with good safety and tolerability: results of the ACTG 5283 study. *Antimicrob Agents Chemother*. Apr 2015;59(4):2094-2101. Available at http://www.ncbi.nlm.nih.gov/pubmed/25624326.
38. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception*. Apr 2012;85(4):425-427. Available at http://www.ncbi.nlm.nih.gov/pubmed/22036046.
39. McCarty EJ, Keane H, Quinn K, Quah S. Implanon(R) failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. *Int J STD AIDS*. Jul 2011;22(7):413-414. Available at http://www.ncbi.nlm.nih.gov/pubmed/21729965.
40. Scarsi KK, Darin KM, Nakalema S, et al. Unintended Pregnancies Observed With Combined Use of the Levonorgestrel Contraceptive Implant and Efavirenz-based Antiretroviral Therapy: A Three-Arm Pharmacokinetic Evaluation Over 48 Weeks. *Clin Infect Dis*. Mar 15 2016;62(6):675-682. Available at http://www.ncbi.nlm.nih.gov/pubmed/26646680.
41. Vieira CS, Bahamondes MV, de Souza RM, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. *J Acquir Immune Defic Syndr*. Aug 1 2014;66(4):378-385. Available at http://www.ncbi.nlm.nih.gov/pubmed/24798768.
42. Patel RC, Onono M, Gandhi M, et al. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study. *Lancet HIV*. Nov 2015;2(11):e474-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/26520927.
43. Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. *AIDS*. Mar 13 2014;28(5):791-793. Available at http://www.ncbi.nlm.nih.gov/pubmed/24401645.
44. Morrison CS, Nanda K. Hormonal contraception and HIV: an unanswered question. *Lancet Infect Dis*. Jan 2012;12(1):2-3. Available at http://www.ncbi.nlm.nih.gov/pubmed/21975268.
45. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis*. Jan 2012;12(1):19-26. Available at http://www.ncbi.nlm.nih.gov/pubmed/21975269.
46. World Health Organization. Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statment. Geneva, Switzerland 2014. Available at http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf?ua=1.

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47. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. *Am J Obstet Gynecol*. Aug 2007;197(2):144 e141-148. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17689627.
48. Curtis KM, Nanda K, Kapp N. Safety of hormonal and intrauterine methods of contraception for women with HIV/AIDS: a systematic review. *AIDS*. Nov 2009;23 Suppl 1:S55-67. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20081389.
49. U.S. Medical Eligibility Criteria for Contraceptive Use. Recommendations and Reports June 18, 2010 / 59(RR04);1-6; Prepared by Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion: (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_e). 2010.
50. Heikinheimo O, Lehtovirta P, Aho I, Ristola M, Paavonen J. The levonorgestrel-releasing intrauterine system in human immunodeficiency virus-infected women: a 5-year follow-up study. *Am J Obstet Gynecol*. Feb 2011;204(2):126 e121-124. Available at http://www.ncbi.nlm.nih.gov/pubmed/21035781.
51. Lehtovirta P, Paavonen J, Heikinheimo O. Experience with the levonorgestrel-releasing intrauterine system among HIV-infected women. *Contraception*. Jan 2007;75(1):37-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/17161122.
52. Coleman JS, Mwachari C, Balkus J, et al. Effect of the levonorgestrel intrauterine device on genital HIV-1 RNA shedding among HIV-1-infected women not taking antiretroviral therapy in Nairobi, Kenya. *J Acquir Immune Defic Syndr*. Jun 1 2013;63(2):245-248. Available at http://www.ncbi.nlm.nih.gov/pubmed/23446496.
53. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis*. Feb 15 2001;183(4):539-545. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11170978.
54. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med*. Aug 5 1999;341(6):385-393. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432323.
55. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. Aug 5 1999;341(6):394-402. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10432324.
56. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
57. Gaur AH, Freimanis-Hance L, Dominguez K, et al. Knowledge and practice of prechewing/prewarming food by HIV-infected women. *Pediatrics*. May 2011;127(5):e1206-1211. Available at http://www.ncbi.nlm.nih.gov/pubmed/21482608.
58. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr*. Aug 1 2008;48(4):408-417. Available at http://www.ncbi.nlm.nih.gov/pubmed/18614923.
59. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care*. Sep 2008;20(8):958-968. Available at http://www.ncbi.nlm.nih.gov/pubmed/18608073.
60. Rana AI, Gillani FS, Flanigan TP, Nash BT, Beckwith CG. Follow-up care among HIV-infected pregnant women in Mississippi. *J Womens Health (Larchmt)*. Oct 2010;19(10):1863-1867. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20831428.

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

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

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

Clinical Course of HIV-2 Infection

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

Diagnosis of HIV-2 Infection

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

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

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(http://depts.washington.edu/labweb/AboutLM/Contact.htm)[7] and the New York State Department of Health (http://www.wadsworth.org/divisions/infdis/hiv/Diagnostic_HIV_Testing_Services.html).[8] However, it is important to note that approximately one-quarter to one-third of HIV-2-infected patients without ART will have HIV-2 RNA levels below the limits of detection; some of these patients will have clinical progression and CD4 cell count decline. No validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available for clinical use.

Treatment of HIV-2 Infection

To date, no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection have been completed;[9] thus, the optimal treatment strategy has not been defined. Three clinical trials to assess first-line ART for HIV-2 infection are currently underway; 2 are enrolling patients with CD4 counts <500 cells/mm^3 (NCT016058090 and NCT02180438) and 1 is enrolling patients with CD4 count >200 and ≤600 cells/mm^3 (NCT02150993). Although the optimal CD4 cell count threshold for initiating ART in HIV-2 infection is unknown, therapy should be started before there is clinical progression.

HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTI)[10] and to enfuvirtide (T20).[11] Data from *in vitro* studies suggest that HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1.[12,13] Darunavir (DRV), lopinavir (LPV), and saquinavir (SQV) are more active against HIV-2 than other approved protease inhibitors (PIs);[14-17] one of these boosted PIs should be used if a PI-based regimen is used. Other PIs should be avoided because of their lack of ARV activity and high failure rates. The integrase strand transfer inhibitors (INSTIs) raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) have potent activity against HIV-2.[18-21] The CCR5 antagonist maraviroc (MVC) appears active against some HIV-2 isolates;[22] however, no approved assays to determine HIV-2 co-receptor tropism exist and HIV-2 is known to use many other minor co-receptors in addition to CCR5 and CXCR4.[23]

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

Resistance-associated viral mutations to NRTIs, PIs and/or INSTIs commonly develop in HIV-2 infected patients while on therapy.[24,29,37-40,41] Currently, HIV-2 transmitted drug resistance appears rare.[42] In one small study, DTG was found to have activity as a second-line INSTI in some HIV-2 patients with extensive ARV experience and RAL resistance.[43] Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ between the HIV types.[13,29,44]

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

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

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monitoring. In the event of virologic, immunologic, or clinical failure, second-line treatment should be instituted in consultation with an expert in HIV-2 management.

References

1. Matheron S, Pueyo S, Damond F, et al. Factors associated with clinical progression in HIV-2 infected-patients: the French ANRS cohort. *AIDS*. 2003;17(18):2593-2601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14685053.
2. Marlink R, Kanki P, Thior I, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science*. 1994;265(5178):1587-1590. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7915856.
3. O'Brien TR, George JR, Epstein JS, Holmberg SD, Schochetman G. Testing for antibodies to human immunodeficiency virus type 2 in the United States. *MMWR Recomm Rep*. 1992;41(RR-12):1-9. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1324395.
4. Centers for Disease Control and Prevention, Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Available at http://stacks.cdc.gov/view/cdc/23447.
5. Chan PA, Wakeman SE, Flanigan T, Cu-Uvin S, Kojic E, Kantor R. HIV-2 diagnosis and quantification in high-risk patients. *AIDS Res Ther*. 2008;5:18. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18700986.
6. Damond F, Benard A, Balotta C, et al. An international collaboration to standardize HIV-2 viral load assays: results from the 2009 ACHI(E)V(2E) quality control study. *J Clin Microbiol*. 2011;49(10):3491-3497. Available at http://www.ncbi.nlm.nih.gov/pubmed/21813718.
7. Chang M, Gottlieb GS, Dragavon JA, et al. Validation for clinical use of a novel HIV-2 plasma RNA viral load assay using the Abbott m2000 platform. *J Clin Virol*. 2012;55(2):128-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/22832059.
8. Styer LM, Miller TT, Parker MM. Validation and clinical use of a sensitive HIV-2 viral load assay that uses a whole virus internal control. *J Clin Virol*. 2013;58 Suppl 1:e127-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/24342472.
9. Gottlieb GS, Eholie SP, Nkengasong JN, et al. A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in West Africa. *AIDS*. 2008;22(16):2069-2072; discussion 2073-2064. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18832869.
10. Tuaillon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr*. 2004;37(5):1543-1549. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15577405.
11. Poveda E, Rodes B, Toro C, Soriano V. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses*. 2004;20(3):347-348. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15117459.
12. Boyer PL, Sarafianos SG, Clark PK, Arnold E, Hughes SH. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? *PLoS Pathog*. 2006;2(2):e10. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16485036.
13. Smith RA, Anderson DJ, Pyrak CL, Preston BD, Gottlieb GS. Antiretroviral drug resistance in HIV-2: three amino acid changes are sufficient for classwide nucleoside analogue resistance. *J Infect Dis*. 2009;199(9):1323-1326. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19358668.
14. Parkin NT, Schapiro JM. Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther*. 2004;9(1):3-12. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15040531.
15. Desbois D, Roquebert B, Peytavin G, et al. *In vitro* phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother*. 2008;52(4):1545-1548. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18227188.
16. Brower ET, Bacha UM, Kawasaki Y, Freire E. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. *Chem Biol Drug Des*. 2008;71(4):298-305. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18312292.
17. Rodes B, Sheldon J, Toro C, Jimenez V, Alvarez MA, Soriano V. Susceptibility to protease inhibitors in HIV-2 primary

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isolates from patients failing antiretroviral therapy. *J Antimicrob Chemother*. 2006;57(4):709-713. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16464891.

18. Roquebert B, Damond F, Collin G, et al. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir *in vitro*. *J Antimicrob Chemother*. 2008;62(5):914-920. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18718922.
19. Charpentier C, Larrouy L, Collin G, et al. In-vitro phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitor S/GSK1349572. *AIDS*. 2010;24(17):2753-2755. Available at http://www.ncbi.nlm.nih.gov/pubmed/20827161.
20. Smith RA, Raugi DN, Pan C, et al. Three main mutational pathways in HIV-2 lead to high-level raltegravir and elvitegravir resistance: implications for emerging HIV-2 treatment regimens. PLoS One. 2012;7(9):e45372. Available at http://www.ncbi.nlm.nih.gov/pubmed/23028968.
21. Smith RA, Raugi DN, Pan C, et al. *In vitro* activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. *Retrovirology*. 2015;12(10). Available at http://www.retrovirology.com/content/12/1/10.
22. Visseaux B, Charpentier C, Hurtado-Nedelec M, et al. *In vitro* phenotypic susceptibility of HIV-2 clinical isolates to CCR5 inhibitors. *Antimicrob Agents Chemother*. 2012;56(1):137-139. Available at http://www.ncbi.nlm.nih.gov/pubmed/22064539.
23. Owen SM, Ellenberger D, Rayfield M, et al. Genetically divergent strains of human immunodeficiency virus type 2 use multiple coreceptors for viral entry. *J Virol*. 1998;72(7):5425-5432. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9620997.
24. Gottlieb GS, Badiane NM, Hawes SE, et al. Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resouce-limited West Africa. *Clin Infect Dis*. 2009;48(4):476-483. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19143530.
25. Jallow S, Kaye S, Alabi A, et al. Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in The Gambia. *AIDS*. 2006;20(10):1455-1458. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16791023.
26. Adje-Toure CA, Cheingsong R, Garcia-Lerma JG, et al. Antiretroviral therapy in HIV-2-infected patients: changes in plasma viral load, CD4+ cell counts, and drug resistance profiles of patients treated in Abidjan, Cote d'Ivoire. *AIDS*. 2003;17 Suppl 3:S49-54. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14565609.
27. Cavaco-Silva J, Aleixo MJ, Van Laethem K, et al. Mutations selected in HIV-2-infected patients failing a regimen including atazanavir. *J Antimicrob Chemother*. 2013;68(1):190-192. Available at http://www.ncbi.nlm.nih.gov/pubmed/22977160.
28. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. *AIDS*. 2006;20(3):459-462. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16439883.
29. Ruelle J, Roman F, Vandenbroucke AT, et al. Transmitted drug resistance, selection of resistance mutations and moderate antiretroviral efficacy in HIV-2: analysis of the HIV-2 Belgium and Luxembourg database. *BMC Infect Dis*. 2008;8:21. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18304321.
30. Benard A, Damond F, Campa P, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. *AIDS*. 2009;23(9):1171-1173. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19349850.
31. Ekouevi DK, Balestre E, Coffie PA, et al. Characteristics of HIV-2 and HIV-1/HIV-2 Dually Seropositive Adults in West Africa Presenting for Care and Antiretroviral Therapy: The IeDEA-West Africa HIV-2 Cohort Study. *PLoS One*. 2013;8(6):e66135. Available at http://www.ncbi.nlm.nih.gov/pubmed/23824279.
32. Drylewicz J, Matheron S, Lazaro E, et al. Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. *AIDS*. 2008;22(4):457-468. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18301058.
33. Drylewicz J, Eholie S, Maiga M, et al. First-year lymphocyte T CD4+ response to antiretroviral therapy according to the HIV type in the IeDEA West Africa collaboration. *AIDS*. 2010;24(7):1043-1050. Available at http://www.ncbi.nlm.nih.gov/pubmed/20397306.
34. Peterson K, Ruelle J, Vekemans M, Siegal FP, Deayton JR, Colebunders R. The role of raltegravir in the treatment of HIV-2 infections: evidence from a case series. *Antivir Ther*. 2012;17(6):1097-1100. Available at http://www.ncbi.nlm.nih.gov/pubmed/22892365.

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35. Zheng Y, Lambert C, Arendt V, Seguin-Devaux C. Virological and immunological outcomes of elvitegravir-based regimen in a treatment-naive HIV-2-infected patient. *AIDS*. 2014;28(15):2329-2331. Available at http://www.ncbi.nlm.nih.gov/pubmed/25313590.
36. Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. *BMC Infect Dis*. 2014;14:461. Available at http://www.ncbi.nlm.nih.gov/pubmed/25154616.
37. Damond F, Matheron S, Peytavin G, et al. Selection of K65R mutation in HIV-2-infected patients receiving tenofovir-containing regimen. *Antivir Ther*. 2004;9(4):635-636. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15456096.
38. Raugi DN, Smith RA, Ba S, et al. Complex patterns of protease inhibitor resistance among antiretroviral treatment-experienced HIV-2 patients from Senegal: implications for second-line therapy. *Antimicrob Agents Chemother*. 2013;57(6):2751-2760. Available at http://www.ncbi.nlm.nih.gov/pubmed/23571535.
39. Charpentier C, Eholie S, Anglaret X, et al. Genotypic resistance profiles of HIV-2-treated patients in West Africa. *AIDS*. 2014;28(8):1161-1169. Available at http://www.ncbi.nlm.nih.gov/pubmed/24583671.
40. Charpentier C, Roquebert B, Delelis O, et al. Hot spots of integrase genotypic changes leading to HIV-2 resistance to raltegravir. *Antimicrob Agents Chemother*. 2011;55(3):1293-1295. Available at http://www.ncbi.nlm.nih.gov/pubmed/21189351.
41. Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU: supporting standardized HIV-2 drug resistance interpretation in Europe. *Clin Infect Dis*. 2013;56(11):1654-1658. Available at http://www.ncbi.nlm.nih.gov/pubmed/23429380.
42. Charpentier C, Visseaux B, Benard A, et al. Transmitted drug resistance in French HIV-2-infected patients. *AIDS*. 2013;27(10):1671-1674. Available at http://www.ncbi.nlm.nih.gov/pubmed/23595155.
43. Descamps D, Peytavin G, Visseaux B, et al. Dolutegravir in HIV-2 infected patients with resistant virus to first-line integrase inhibitors from the French Named Patient Program. *Clin Infect Dis*. 2015. Available at http://www.ncbi.nlm.nih.gov/pubmed/25690598.
44. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med*. 2010;11(10):611-619. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20961377.
45. New York State Department of Health AIDS Institute. Human Immunodeficiency Virus Type 2 (HIV-2). 2012. Available at http://www.hivguidelines.org/wp-content/uploads/2014/04/human-immunodeficiency-virus-type-2-hiv-2.pdf. Accessed March 10, 2015.
46. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. Available at http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. Accessed March 10, 2015.
47. Expert Group on the Medical Management of HIV Infected Individuals with the Ministry of Health and Sports. French HIV-2 Guidelines. 2010. Available at http://www.sante.gouv.fr/IMG/pdf/Rapport_2010_sur_la_prise_en_charge_medicale_des_personnes_infectees_par_le_VIH_sous_la_direction_du_Pr-_Patrick_Yeni.pdf. Accessed February 9, 2015
48. World Health Organization. What ARV regimen to start with in adults adolescents and pregnant women living with HIV-2? 2013. Available at http://apps.who.int/iris/bitstream/10665/90772/1/WHO_HIV_2013.36_eng.pdf?ua=1. Accessed February 9, 2015.

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

Key Considerations When Caring for Older HIV-Infected Patients Receiving Antiretroviral Therapy (ART)
• 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 HIV-infected patients than in younger HIV-infected patients. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older HIV-infected patients should be monitored closely. • Polypharmacy is common in older HIV patients; 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 HIV-infected patients 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 HIV-infected patient.
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 HIV-infected individuals, resulting in an increasing number of older individuals living with HIV infection. In the United States, among persons living with HIV infection 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 HIV-infected patients 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 HIV-infected patients 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 post-menopausal 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 HIV infection, 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

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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 decreases 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 HIV-uninfected older adults, 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 HIV-infected patients 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 HIV patients are accumulating,[17,18] the age of diagnosis for myocardial infection and non-AIDS cancers in HIV-infected and HIV-uninfected patients is the same.[18,19]
- Older HIV patients have a greater incidence of complications and co-morbidities than HIV-uninfected adults of similar age, 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 the HIV population.

Initiating Antiretroviral Therapy in the Older HIV Patient

ART is recommended for all HIV-infected individuals (**AI**; see Initiation of Antiretroviral Therapy section). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population. In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (patients between ages 45 and 65 years).[21] No data support a preference for any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of patient age. The choice of regimen should instead be informed by a comprehensive review of the patient's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an antiretroviral regimen based on an older patient's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older patients with reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix Table 7). In addition, ARV regimen selection may be influenced by potential interaction of antiretroviral medications with drugs used concomitantly to manage co-morbidities (see Tables 18-20b). Adults age >50 years should be monitored for ART effectiveness and safety similarly to other HIV-infected populations [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 14).

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.

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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.

HIV-infected patients with 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 HIV-infected patients 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 HIV-negative older patients, polypharmacy is a major cause of iatrogenic complications.[27] Some of these complications may be caused by medication errors (by prescribers or patients), medication non-adherence, additive drug toxicities, and drug-drug interactions. Older HIV-infected patients are probably at an even greater risk of polypharmacy-related adverse consequences than younger HIV-infected or similarly aged HIV-uninfected patients. When evaluating any new clinical complaint or laboratory abnormality in HIV-infected patients, 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, HIV-uninfected participants with normal organ function (see Tables 18-20b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be greater in older HIV-infected patients than in younger HIV-infected patients.

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 non-adherence may be more prevalent in older patients, some studies have shown that older HIV-infected patients 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 Antiretroviral Therapy).

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 HIV-infected adults 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 HIV-infected patients 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

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HIV-infected adults.[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 HIV-infected older patients.[44-48]

Switching, Interrupting, and Discontinuing Antiretroviral Therapy in Older Patients

Given the greater incidence of co-morbidities, non-AIDS complications and frailty among older HIV-infected patients, 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 HIV-infected patients 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 HIV populations 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 HIV infected patients, increasing the number of patients >50 years of age living with HIV. However, unique challenges in this population include greater incidence of complications and co-morbidities, 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 HIV-infected patients is warranted.

References

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2014; vol. 26. 2015. Available at http://www.cdc.gov/hiv/library/reports/surveillance/. Accessed December 10, 2015.
2. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009;338:a3172. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19171560.
3. Levy JA, Ory MG, Crystal S. HIV/AIDS interventions for midlife and older adults: current status and challenges. *J Acquir Immune Defic Syndr*. Jun 1 2003;33 Suppl 2:S59-67. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12853854.
4. Levy BR, Ding L, Lakra D, Kosteas J, Niccolai L. Older persons' exclusion from sexually transmitted disease risk-reduction clinical trials. *Sex Transm Dis*. Aug 2007;34(8):541-544. Available at

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17297381.

5. Althoff KN, Gebo KA, Gange SJ, et al. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? *AIDS Res Ther*. 2010;7:45. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21159161.
6. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2013. HIV Surveillance Supplemental Report 2015;20 (No. 2). 2015. Available at http://www.cdc.gov/hiv/library/reports/surveillance/. Accessed August 21, 2015.
7. Lodi S, Phillips A, Touloumi G, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. *Clin Infect Dis*. Oct 2011;53(8):817-825. Available at http://www.ncbi.nlm.nih.gov/pubmed/21921225.
8. Sabin CA, Smith CJ, d'Arminio Monforte A, et al. Response to combination antiretroviral therapy: variation by age. *AIDS*. Jul 31 2008;22(12):1463-1473. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614870.
9. Stone VE, Bounds BC, Muse VV, Ferry JA. Case records of the Massachusetts General Hospital. Case 29-2009. An 81-year-old man with weight loss, odynophagia, and failure to thrive. *N Engl J Med*. Sep 17 2009;361(12):1189-1198. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19759382.
10. Ward EG, Disch WB, Schensul JJ, Levy JA. Understanding low-income, minority older adult self-perceptions of HIV risk. *J Assoc Nurses AIDS Care*. Jan-Feb 2011;22(1):26-37. Available at http://www.ncbi.nlm.nih.gov/pubmed/20580270.
11. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. Sep 22 2006;55(RR-14):1-17. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16988643.
12. Ford CL, Godette DC, Mulatu MS, Gaines TL. Recent HIV testing prevalence, determinants, and disparities among U.S. older adult respondents to the behavioral risk factor surveillance system. *Sex Transm Dis*. Aug 2015;42(8):405-410. Available at http://www.ncbi.nlm.nih.gov/pubmed/26165428.
13. Martin J, Volberding P. HIV and premature aging: A field still in its infancy. *Ann Intern Med*. Oct 5 2010;153(7):477-479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20921548.
14. Liu JC, Leung JM, Ngan DA, et al. Absolute leukocyte telomere length in HIV-infected and uninfected individuals: evidence of accelerated cell senescence in HIV-associated chronic obstructive pulmonary disease. *PLoS One*. 2015;10(4):e0124426. Available at http://www.ncbi.nlm.nih.gov/pubmed/25885433.
15. Zanet DL, Thorne A, Singer J, et al. Association between short leukocyte telomere length and HIV infection in a cohort study: No evidence of a relationship with antiretroviral therapy. *Clin Infect Dis*. May 2014;58(9):1322-1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/24457340.
16. Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PLoS One*. 2014;9(5):e97482. Available at http://www.ncbi.nlm.nih.gov/pubmed/24830290.
17. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis*. Dec 15 2014;59(12):1787-1797. Available at http://www.ncbi.nlm.nih.gov/pubmed/25182245.
18. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin Infect Dis*. Feb 15 2015;60(4):627-638. Available at http://www.ncbi.nlm.nih.gov/pubmed/25362204.
19. Rasmussen LD, May MT, Kronborg G, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. *Lancet HIV*. Jul 2015;2(7):e288-298. Available at http://www.ncbi.nlm.nih.gov/pubmed/26423253.
20. Althoff KN, Jacobson LP, Cranston RD, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. *J Gerontol A Biol Sci Med Sci*. Feb 2014;69(2):189-198. Available at http://www.ncbi.nlm.nih.gov/pubmed/24127428.
21. Edwards JK, Cole SR, Westreich D, et al. Age at Entry Into Care, Timing of Antiretroviral Therapy Initiation, and 10-Year Mortality Among HIV-Seropositive Adults in the United States. *Clin Infect Dis*. Oct 1 2015;61(7):1189-1195. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082505.
22. Horberg MA, Hurley LB, Klein DB, et al. The HIV Care Cascade Measured Over Time and by Age, Sex, and Race in a

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Large National Integrated Care System. *AIDS Patient Care STDS*. Nov 2015;29(11):582-590. Available at http://www.ncbi.nlm.nih.gov/pubmed/26505968.

23. Althoff KN, Justice AC, Gange SJ, et al. Virologic and immunologic response to HAART, by age and regimen class. *AIDS*. Oct 23 2010;24(16):2469-2479. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20829678.
24. Bosch RJ, Bennett K, Collier AC, Zackin R, Benson CA. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. Mar 1 2007;44(3):268-277. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17146370.
25. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis*. 2006;6:159. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17087819.
26. Sitar DS. Aging issues in drug disposition and efficacy. *Proc West Pharmacol Soc*. 2007;50:16-20. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18605223.
27. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium". *JAMA*. Oct 13 2010;304(14):1592-1601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20940385.
28. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother*. Sep 2011;66(9):2107-2111. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21680580.
29. Wellons MF, Sanders L, Edwards LJ, Bartlett JA, Heald AE, Schmader KE. HIV infection: treatment outcomes in older and younger adults. *J Am Geriatr Soc*. Apr 2002;50(4):603-607. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11982658.
30. Wutoh AK, Elekwachi O, Clarke-Tasker V, Daftary M, Powell NJ, Campusano G. Assessment and predictors of antiretroviral adherence in older HIV-infected patients. *J Acquir Immune Defic Syndr*. Jun 1 2003;33 Suppl 2:S106-114. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12853859.
31. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP, Jr. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med*. Apr 9 2007;167(7):684-691. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17420427.
32. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother*. Feb 2011;9(1):11-23. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21459305.
33. Justice AC. HIV and aging: time for a new paradigm. *Curr HIV/AIDS Rep*. May 2010;7(2):69-76. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20425560.
34. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. Sep 2006;43(1):27-34. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16878047.
35. Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS*. Mar 21 2006;20(5):741-749. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16514305.
36. Vance DE, Wadley VG, Crowe MG, Raper JL, Ball KK. Cognitive and everyday functioning in older and younger adults with and without HIV. *Clinical Gerontologists* 2011;34(5):413-426.
37. Jacks A, Wainwright DA, Salazar L, et al. Neurocognitive deficits increase risk of poor retention in care among older adults with newly diagnosed HIV infection. *AIDS*. Aug 24 2015;29(13):1711-1714. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372282.
38. Grov C, Golub SA, Parsons JT, Brennan M, Karpiak SE. Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care*. May 2010;22(5):630-639. Available at http://www.ncbi.nlm.nih.gov/pubmed/20401765.
39. Kalichman SC, Heckman T, Kochman A, Sikkema K, Bergholte J. Depression and thoughts of suicide among middle-aged and older persons living with HIV-AIDS. *Psychiatr Serv*. Jul 2000;51(7):903-907. Available at http://www.ncbi.nlm.nih.gov/pubmed/10875956.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

40. Kochanek KD, Xu J, Murphy SL, Minino AM, King HC. Deaths: Preliminary data for 2009. *National Vital Statistics Report*s. 2011;59(4):1-54. Available at

41. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. Dec 2011;53(11):1120-1126. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998278.

42. Capeau J. Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. *Clin Infect Dis*. Dec 2011;53(11):1127-1129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998279.

43. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis*. Dec 2011;53(11):1130-1139. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21998280.

44. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):e1-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/24235263.

45. Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis*. Apr 15 2015;60(8):1242-1251. Available at http://www.ncbi.nlm.nih.gov/pubmed/25609682.

46. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Nov 1 2014;59(9):e96-138. Available at http://www.ncbi.nlm.nih.gov/pubmed/25234519.

47. American Academy of HIV Medicine. The HIV and Aging Consensus Project: Recommended treatment strategies for clinicians managing older patients with HIV. 2011. Available at http://www.aahivm.org/Upload_Module/upload/HIV%20and%20Aging/Aging%20report%20working%20document%20FINAL.pdf. Accessed January 13, 2016.

48. Jacobson TA, Maki KC, Orringer CE, al. e. National lipid association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol*. 2015.

49. Selwyn PA. Chapter 75. In: Berger AM S, JL, Von Roenn JH, ed. Palliative care in HIV/AIDS. In Principles and Practice of Palliative Care and Supportive Oncology 3rd Edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2007:833-848.

50. Harding R, Simms V, Krakauer E, et al. Quality HIV Care to the End of life. *Clin Infect Dis*. Feb 15 2011;52(4):553-554; author reply 554. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21258107.

51. Brennan A, Morley D, O'Leary AC, Bergin CJ, Horgan M. Determinants of HIV outpatient service utilization: a systematic review. *AIDS Behav*. Jan 2015;19(1):104-119. Available at http://www.ncbi.nlm.nih.gov/pubmed/24907780.

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Considerations for Antiretroviral Use in Patients with Coinfections

Hepatitis B (HBV)/HIV Virus Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

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, for patients coinfected with HIV and HBV, ART should be initiated with the fixed-dose combination of TDF/FTC or TAF/FTC, or the individual drug combinations of TDF plus 3TC 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 used in HBV/HIV-coinfected patients **(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 HBV/HIV coinfected patients **(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 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)**.
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 HIV-infected persons 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 HBV/HIV-infected persons 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 HBV/HIV-coinfected patients not on ART, the drug may select for the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, when used in HBV/HIV-coinfected patients, 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 HBV/HIV coinfected patients, 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]

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- In HBV/HIV coinfected patients, immune reconstitution following initiation of treatment for HIV, HBV, or both can be associated with elevated transaminase levels, possibly because HBV 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. However, increased transaminase levels in HBV/HIV-coinfected persons 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 HBV/HIV-Coinfected Patients

- All patients with chronic HBV should be evaluated to assess the severity of HBV infection (see the HBV section of 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 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 NRTIs is to prevent liver disease complications by sustained suppression of HBV replication.

Antiviral 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 HBV-monoinfected patients 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; $P = 0.47$).[16] TAF was also noninferior to TDF in HBeAg-positive patients with chronic HBV monoinfection with similar percentage of patients achieving HBV DNA levels <29 IU/ml at 48 weeks of therapy (64% for TAF vs. 67% for TDF; $P = 0.25$).[17] In both studies, patients on TAF experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at week 48 than patients receiving TDF. The median change in estimated glomerular filtration rate (eGFR) from baseline to week 48 also favored TAF.[16,17]

In HBV/HIV-coinfected patients, only TDF (with FTC or 3TC) or TAF/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.

Recommended Therapy

The combination of TDF (with FTC or 3TC) or TAF/FTC should be used as the NRTI backbone of an ARV regimen and for the treatment of both HIV and HBV infection[18-20] **(AII)**. The decision whether to use a TAF- or TDF-containing regimen should be based on an assessment of risk for nephrotoxicity and for acceleration of bone loss. In a switch study in HBV/HIV-coinfected patients, study participants who switched from a

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primarily TDF-based ART regimen to the fixed-dose combination EVG/c/TAF/FTC maintained or achieved HBV suppression, with improved eGFR and bone turnover markers.[21] Currently TAF/FTC-containing regimens 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 HBV/HIV-coinfected patients 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[22] **(BII)**. Because entectavir 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 HBV/HIV-coinfected patients. 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 HBV/HIV-coinfected persons with decompensated cirrhosis.

Not Recommended Therapy

Other HBV treatment regimens include adefovir in combination with 3TC or FTC, or telbivudine in addition to a fully suppressive ARV regimen.[18,23,24] However, data on these regimens in persons with HBV/HIV coinfection are limited. In addition, compared to TDF, TAF, or entecavir, these regimens are associated with a higher incidence of toxicity, including renal disease when used with adefovir and myopathy and neuropathy when used with telbivudine, as well as higher rates of HBV treatment failure. Therefore, the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents does not currently recommend ADV or telbivudine for HBV/HIV-coinfected patients.

- **Need to discontinue 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)**.

References

1. Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat*. Feb 11 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20158604.
2. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. Dec 14 2002;360(9349):1921-1926. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12493258.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. Mar 24 2005;19(6):593-601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15802978.

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4. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS*. Sep 10 2009;23(14):1881-1889. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19550291.
5. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med*. Jan 2009;10(1):12-18. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18795964.
6. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *AIDS*. Oct 17 2003;17(15):2191-2199. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14523276.
7. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. Jul 1 2002;186(1):23-31. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12089658.
8. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS*. Mar 27 2010;24(6):857-865. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20216301.
9. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med*. Jun 21 2007;356(25):2614-2621. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17582071.
10. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology*. Nov 1999;30(5):1302-1306. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10534354.
11. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis*. Jan 2001;32(1):144-148. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11118394.
12. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. Jan 5 2000;283(1):74-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10632283.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. Dec 22 2000;14(18):2895-2902. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153671.
14. Neukam K, Mira JA, Collado A, et al. Liver Toxicity of Current Antiretroviral Regimens in HIV-Infected Patients with Chronic Viral Hepatitis in a Real-Life Setting: The HEPAVIR SEG-HEP Cohort. *PLoS One*. 2016;11(2):e0148104. Available at http://www.ncbi.nlm.nih.gov/pubmed/26848975.
15. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed June 22, 2016.
16. Buti M, Gane E, Seto WK, al. e. A Phase 3 Study of Tenofovir Alafenamide Compared With Tenofovir Disoproxil Fumarate in Patients With HBeAg-Negative, Chronic Hepatitis B: Week 48 Efficacy and Safety Results. EASL International Liver Conference; 2016; Barcelona, Spain.
17. Chan HLY, Fung S, Seto WK. A Phase 3 Study of Tenofovir Alafenamide Compared With Tenofovir Disoproxil Fumarate in Patients With HBeAg-Positive, Chronic Hepatitis B: Week 48 Efficacy and Safety Results. EASL International Liver Conference; 2016; Barcelona, Spain.
18. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. Nov 2006;44(5):1110-1116. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17058225.
19. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. Aug 24 2009;23(13):1707-1715. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19584701.
20. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-Term Therapy with Tenofovir is Effective for Patients Co-

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Infected with HIV and HBV. *Gastroenterology*. Aug 26 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20801123.

21. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) in HIV-1/Hepatitis B Coinfected Adults. *J Acquir Immune Defic Syndr*. May 11 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/27171740.
22. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfected patients receiving lamivudine as part of antiretroviral therapy. *AIDS*. Sep 12 2008;22(14):1779-1787. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753861.
23. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet*. Sep 1 2001;358(9283):718-723. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11551579.
24. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*. 2008;13(7):895-900. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19043923.

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HIV/Hepatitis C Virus Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel Recommendations
• All HIV-infected patients should be screened for hepatitis C virus (HCV) infection. Patients at high risk of HCV infection should be screened annually and whenever HCV infection is suspected. • 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 HCV/HIV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Therefore, ART should be initiated in all HCV/HIV-coinfected patients, regardless of CD4 T lymphocyte (CD4) cell count **(AI)**. • Initial ART regimens recommended for most HCV/HIV-coinfected patients are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the regimen should be selected with special considerations of potential drug-drug interactions and overlapping toxicities with the HCV treatment regimen (see discussion in the text below and in Table 12). • Combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden, and toxicities. Although ART should be initiated for all HCV/HIV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until HCV treatment is completed **(CIII)**. • In patients with lower CD4 counts (eg, <200 cells/mm^3), ART should be initiated promptly **(AI)** and HCV therapy may be delayed until the patient is stable on HIV treatment **(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 treatment of hepatitis C virus (HCV) infection is rapidly evolving. Data suggest that HCV/HIV-coinfected patients treated with all-oral HCV regimens have sustained virologic response rates comparable to those of HCV-monoinfected patients. The purpose of this section is to discuss 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, please refer to http://www.hcvguidelines.org/.

Among patients with chronic HCV infection, approximately one-third progress to cirrhosis, at a median time of less than 20 years.[1,2] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[3-6] A meta-analysis found that HCV/HIV-coinfected patients had a three-fold greater risk of progression to cirrhosis or decompensated liver disease than HCV-monoinfected patients.[5] The risk of progression is even greater in HCV/HIV-coinfected patients with low CD4 T lymphocyte (CD4) cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in HCV/HIV-coinfected patients, several studies have demonstrated that the rate continues to exceed that observed in patients without HIV infection.[7,8] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[9] is unclear. Although some older ARV drugs that are no longer commonly used have been associated with higher rates of hepatotoxicity in patients with chronic HCV infection,[10,11] newer ARV agents currently in use appear to be less hepatotoxic.

For more than a decade, the mainstay of treatment for HCV infection was a combination regimen of peginterferon and ribavirin (PegIFN/RBV), but this regimen was associated with a poor rate of sustained virologic response (SVR), especially in HCV/HIV-coinfected patients. Rapid advances in HCV drug development led to the discovery of new classes of direct-acting antiviral (DAA) agents that target the HCV replication cycle. Recently approved DAA agents are used with or without RBV and have higher SVR rates, reduced pill burden, less frequent dosing, fewer side effects, and shorter durations of therapy than earlier approved agents.[12-16] Guidance on the treatment and management of HCV in HIV-infected and HIV-uninfected adults can be found at http://www.hcvguidelines.org/.[17]

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Assessment of Hepatitis C Virus/HIV Coinfection

- All HIV-infected patients should be screened for HCV infection using sensitive immunoassays licensed for the detection of antibody to HCV in blood.[18] At-risk HCV-seronegative patients should undergo repeat testing annually. 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 most updated HCV guidelines (see http://www.hcvguidelines.org/).
- 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. HCV/HIV-coinfected patients who are susceptible to hepatitis A virus (HAV) or hepatitis B virus (HBV) infection should be vaccinated against these viruses.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy.

Antiretroviral Therapy in Hepatitis C Virus/HIV Coinfection

When to Start Antiretroviral Therapy

The rate of liver disease (liver fibrosis) progression is accelerated in HCV/HIV-coinfected patients, particularly in individuals with low CD4 counts (≤350 cells/mm^3). Data largely from retrospective cohort studies are inconsistent regarding the effect of ART on the natural history of HCV disease;[6,19,20] however, some studies suggest that ART may slow the progression of liver disease by preserving or restoring immune function and by reducing HIV-related immune activation and inflammation.[21-23] Therefore, ART should be initiated in all HCV/HIV-coinfected patients, regardless of CD4 count **(AI)**. However, in HIV treatment-naive patients with CD4 counts >500 cells/mm^3, some clinicians may choose to defer ART until HCV treatment is completed to avoid drug-drug interactions **(CIII)**. Compared to patients with CD4 counts >350 cells/mm^3, those with CD4 counts <200 cells/mm^3 had lower HCV treatment response rates and higher rates of toxicity due to PegIFN/RBV.[24] There is a lack of data regarding HCV treatment response to combination therapy with DAA agents in those with advanced immunosuppression. For patients with lower CD4 counts (eg, <200 cells/mm^3), ART should be initiated promptly **(AI)** and HCV therapy may be delayed until the patient is stable on HIV treatment **(CIII)**.[25-28]

Antiretroviral Drugs to Start and Avoid

Initial ARV combination regimens recommended for most HIV treatment-naive patients with HCV are the same as those recommended for patients without HCV infection. Special considerations for ARV selection in HCV/HIV-coinfected patients include the folllowing:

- When both HIV and HCV treatments are indicated, the ARV regimen should be selected with careful consideration of potential drug-drug interactions (see Table 12) and overlapping toxicities with the HCV treatment regimen.
- Cirrhotic patients should be carefully evaluated by an expert in advanced liver disease for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. This assessment is necessary because 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 7).

Hepatotoxicity

Drug-induced liver injury (DILI) following the initiation of ART is more common in HCV/HIV-coinfected patients than in those with HIV monoinfection. HVC/HIV coinfected individuals with advanced liver disease (eg, cirrhosis, end-stage liver disease) are at greatest risk for DILI.[29] Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[30]

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- Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. The incidence of significant elevations in liver enzyme levels (more than 5 times the upper limit of the normal laboratory reference range) is low with currently recommended ART regimens. Hypersensitivity (or allergic) reactions associated with rash and elevations in liver enzymes can occur with certain ARVs. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 2 to 8 weeks after initiation of ART and every 3 to 6 months thereafter. Mild to moderate fluctuations in ALT and/or AST 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. Patients with significant ALT and/or AST elevation should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (eg, acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis). Short-term interruption of the ART regimen or of the specific drug suspected of causing the DILI may be required.[31]

Concurrent Treatment of HIV and Hepatitis C Virus Infection

Concurrent treatment of HIV and HCV is feasible, but treatment may be complicated by pill burden, drug-drug interactions, and toxicities. In this context, the stage of HCV disease should be assessed to determine the medical need for HCV treatment and to inform the decision on when to start treatment. Additional guidance on the treatment and management of HCV in HIV-infected and uninfected adults can be found at http://www.hcvguidelines.org/. If the decision is to treat HCV, the ART regimen may need to be modified before HCV treatment is initiated to reduce the potential for drug-drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment. See Table 12 for recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection. In patients with suppressed plasma HIV RNA and modified ART, HIV RNA should be measured within 4 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After HCV treatment is completed, the modified ART regimen should be continued for at least 2 weeks before reinitiating the original regimen. Continued use of the modified regimen is necessary because of the prolonged half-life of some HCV drugs and the potential risk of drug-drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed.

Antiretroviral and Hepatitis C Virus Drug-Drug Interactions

Considerations for the concurrent use of ART and recommended HCV agents (per http://hcvguidelines.org/) are discussed below. Table 12 provides recommendations on the concomitant use of selected drugs for treatment of HCV and HIV infection.

- Sofosbuvir is an HCV NS5B nucleotide polymerase inhibitor that is not metabolized by the cytochrome P450 enzyme system and, therefore, can be used in combination with most ARV drugs. Sofosbuvir is a substrate of p-glycoprotein (P-gp). P-gp inducers, such as tipranavir (TPV), may decrease sofosbuvir plasma concentrations and should not be coadministered with sofosbuvir. No other clinicially significant pharmocokinetic interactions between sofosbuvir and ARVs have been identified.

- Ledipasvir is an HCV NS5A inhibitor and is part of a fixed-dose drug combination of sofosbuvir and ledipasvir.[32] Similar to sofosbuvir, ledipasvir is not metabolized by the cytochrome P (CYP) 450 system of enzymes and is a substrate for P-gp. Ledipasvir inhibits the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. The use of P-gp inducers is not recommended with ledipasivir/sofosbuvir. Coadministering ledipasvir/sofosbuvir and ARV regimens containing tenofovir disoproxil fumarate (TDF) is associated with increased exposure to TDF, especially when TDF is taken with an HIV protease inhibitor (PI) boosted with either ritonavir (RTV) or cobicistat (COBI). In some patients, alternative HCV or ARV drugs should be considered to avoid increases in TDF exposures. If the drugs are coadministered, the patient should be monitored for potential TDF-associated renal injury by assessing measurements of renal function (ie, estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein) before HCV treatment initiation and periodically during treatment.

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- Daclatasvir is an HCV NS5A inhibitor that is approved for use with sofosbuvir.[33] Daclatasvir is a substrate of CYP3A and an inhibitor of P-gp, OATP1B1/3, and BCRP. Moderate or strong inducers of CYP3A, such as efavirenz (EFV), etravirine (ETR), and nevirapine (NVP), may decrease plasma levels of daclatasvir and reduce the drug's therapeutic effect. In this case, the daclatasvir dosage should be increased from 60 mg once daily to 90 mg once daily. By contrast, strong CYP3A inhibitors may increase plasma levels of daclatasvir, in which case the daclatasvir dosage should be reduced to 30 mg once daily. Clinically relevant interactions between daclatasvir and TDF have not been observed. Because daclatasvir also is an inhibitor of P-gp, OATP1B1/3, and BCRP, administration of daclatasvir may increase systemic exposure to medications that are substrates of these transporters and proteins, which could increase or prolong the therapeutic or adverse effects of that medication.

- Elbasvir (a NS5A inhibitor) and grazoprevir (an HCV PI) are available in combination as a fixed-dose tablet. Both elbasvir and grazoprevir are substrates of CYP3A and P-gp.[34] In addition, grazoprevir is a substrate of OATP1B1/3 transporters. Coadministration of the elbasvir and grazoprevir combination with strong CYP3A inducers, such as EFV, is contraindicated because elbasvir and grazoprevir concentrations may be decreased. Coadministration of strong CYP3A4 inhibitors with elbasvir and grazoprevir is also contraindicated or not recommended bcause elbasvir and grazoprevir concentrations may increase. Elbasvir and grazoprevir are also inhibitors of the drug transporter BCRP and may increase plasma concentrations of coadministered BCRP substrates.

- The fixed-dose drug combination of ombitasvir (a NS5A inhibitor), paritaprevir (an HCV PI), and RTV (a pharmacokinetic [PK] enhancer) is copackaged with or without dasabuvir, an NS5B inhibitor.[35,36]
  - Paritaprevir is a substrate and inhibitor of the CYP3A4 enzymes and therefore may have significant interactions with certain ARVs that are metabolized by, or may induce or inhibit, the same pathways. Paritaprevir is also a substrate and inhibitor of OATP1B1/3.
  - Both ombitasvir and paritaprevir are inhibitors of UGT1A1 and also substrates of P-gp and BCRP.
  - Dasabuvir is primarily metabolized by the CYP2C8 enzymes. It is also an inhibitor of UGT1A1 and a substrate of P-gp and BCRP.
  - Coadministration of ombitasvir/paritaprevir/RTV with drugs that are substrates or inhibitors of the enzymes and drug transporters noted may result in increased plasma concentrations of either the HCV drugs or the coadministered drug. Given that several CYP enzymes and drug transporters are involved in the metabolism of ombitasvir, paritaprevir, and RTV, complex drug-drug interactions are likely. Therefore, clinicians need to consider all coadministered drugs for potential drug-drug interactions.
  - If a patient's ART regimen contains RTV- or COBI-boosted atazanavir (ATV), the boosting agent should be discontinued during therapy with ombitasvir/paritaprevir/RTV and ATV should be taken in the morning at the same time as the HCV therapy. RTV or COBI should be restarted after completion of HCV treatment. HIV-infected patients not on ART should be placed on an alternative HCV regimen because RTV has activity against HIV.

- Simeprevir is an HCV NS3/4A PI that is approved for use with sofosbuvir. Simeprevir is a substrate and inhibitor of CYP3A4 and P gp enzymes, and therefore has significant interactions with ARVs that are metabolized by the same pathways (eg, HIV PIs, EFV, ETR). Simeprevir is also an inhibitor of the drug transporter OATP1B1/3.

Given that the treatment of HCV is rapidly evolving, this section will be updated when new HCV drugs that may impact the treatment of HIV are approved. For guidance on the treatment of HCV infection, refer to http://www.hcvguidelines.org/.

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Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 1 of 3)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV direct-acting antiviral (DAA) drugs are based on available pharmacokinetics interaction data or 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 HCV guidelines (www.hcvguidelines.org/) for updated information.

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[b]	Simeprevir
Nucleoside Reverse Transcriptase Inhibitors						
3TC	✓	✓	✓	✓	✓	✓
ABC	✓	✓	✓	✓	✓	✓
FTC	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓ Monitor for TDF toxicity.	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
HIV Protease Inhibitors						
ATV (unboosted)	✓	✓	✓	×	✓ Reduce ATV dose to 300 mg and take in the morning at same time as ombitasvir/ paritaprevir/ritonavir plus dasabuvir. If RTV cannot be used, choose an alternative HCV regimen.	×

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Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 2 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
HIV Protease Inhibitors, continued						
ATV/r or ATV/c	✓ ↓ DCV dose to 30 mg/day	✓	✓ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnote[c]).	×	✓ Take ATV 300 mg in the morning at same time as ombitasvir/ paritaprevir/r plus dasubuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed.	×
DRV/r or DRV/c	✓	✓		×	×	×
FPV or FPV/r	✓	✓		×	×	×
LPV/r	✓	✓		×	×	×
SQV/r	✓ ↓ DCV dose to 30 mg/day			×	×	×
TPV/r	?	×	×	×	×	×
Non-Nucleoside Reverse Transcriptase Inhibitors						
EFV	✓ ↑ DCV dose to 90 mg/day	✓	✓ If used with TDF, monitor for TDF toxicity.	×	×	×
ETR	↑ DCV dose to 90 mg/day	✓		×	×	×
NVP	↑ DCV dose to 90 mg/day	✓		×	×	×
RPV	✓	✓		✓	×	✓

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Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults (page 3 of 3)

Selected HIV Drugs	HCV DAA Drugs					
	NS5A Inhibitor	NS5B Inhibitor	Coformulated NS5A/NS5B Inhibitor	Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor	Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor	NS3A/4A Protease Inhibitor[a]
	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir	Simeprevir
Integrase Strand Transfer Inhibitors						
DTG	✓	✓	✓ If used with TDF, monitor for TDF toxicity.	✓	✓	✓
EVG/c/TDF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	×	×	×	×
EVG/c/TAF/FTC	✓ ↓ DCV dose to 30 mg/day	✓	✓	×	×	×
EVG (plus PI/r without COBI)	✓ ↓ DCV dose to 30 mg/day for all PI/r, except TPV/r — do not coadminister	Refer to Recommendations for individual ritonavir-boosted PI.				
RAL	✓	✓	✓	✓	✓	✓
CCR5 Antagonist						
MVC	✓	✓	✓	?	×	✓

[a] Since boceprevir is no longer recommended for HCV treatment and telaprevir is no longer available in the United States, these products have been removed from this table.

[b] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir.

[c] Consider alternative HCV or ARV therapy to avoid increases in TDF exposure. If coadministration is necessary, monitor for TDF-associated adverse reactions.

Key to Symbols: ✓ = ARV agents that can be used concomitantly

× = ARV agents not recommended

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; c or COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HCV = hepatitis C virus; 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/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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References

1. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med*. Dec 31 1992;327(27):1899-1905. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1280771.
2. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. Jul 26 2000;284(4):450-456. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10904508.
3. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. Mar 22 1997;349(9055):825-832. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9121257.
4. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. Sep 1998;28(3):805-809. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9731576.
5. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. Aug 15 2001;33(4):562-569. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11462196.
6. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS*. Oct 1 2008;22(15):1979-1991. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18784461.
7. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. Aug 14-28 2006;166(15):1632-1641. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16908797.
8. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. Apr 30 2009;360(18):1815-1826. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19339714.
9. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet*. Nov 25 2000;356(9244):1800-1805. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11117912.
10. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. Jan 5 2000;283(1):74-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10632283.
11. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35(1):182-189. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11786975&dopt=Abstract.
12. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. May 15 2014;370(20):1889-1898. Available at http://www.ncbi.nlm.nih.gov/pubmed/24725239.
13. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. May 15 2014;370(20):1879-1888. Available at http://www.ncbi.nlm.nih.gov/pubmed/24720702.
14. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. Jan 16 2014;370(3):211-221. Available at http://www.ncbi.nlm.nih.gov/pubmed/24428467.
15. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. Apr 24 2014;370(17):1594-1603. Available at http://www.ncbi.nlm.nih.gov/pubmed/24720703.
16. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. Jun 23 2011;364(25):2417-2428. Available at http://www.ncbi.nlm.nih.gov/pubmed/21696308.
17. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at http://www.hcvguidelines.org.
18. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and

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Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed July 6, 2016.

19. Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. *AIDS*. Oct 18 2007;21(16):2209-2216. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18090048.
20. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. *J Hepatol*. Jan 2006;44(1):47-55. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16182404.
21. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology*. Oct 2009;50(4):1056-1063. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19670415.
22. Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? *BMC Res Notes*. 2008;1:46. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18710499.
23. Ragni MV, Nalesnik MA, Schillo R, Dang Q. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia*. Mar 2009;15(2):552-558. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19347994.
24. Opravil M, Sasadeusz J, Cooper DA, et al. Effect of baseline CD4 cell count on the efficacy and safety of peginterferon Alfa-2a (40KD) plus ribavirin in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr*. Jan 1 2008;47(1):36-49. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18156990.
25. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. Apr 2009;49(4):1335-1374. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19330875.
26. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS*. May 31 2007;21(9):1073-1089. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17502718.
27. Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol*. Oct 2005;100(10):2338-2354. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16181388.
28. Avidan NU, Goldstein D, Rozenberg L, et al. Hepatitis C viral kinetics during treatment with peg IFN-alpha-2b in HIV/HCV coinfected patients as a function of baseline CD4+ T-cell counts. *J Acquir Immune Defic Syndr*. Dec 1 2009;52(4):452-458. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19797971.
29. Aranzabal L, Casado JL, Moya J, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis*. Feb 15 2005;40(4):588-593. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15712082.
30. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis*. Sep 1 2007;196(5):670-676. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17674307.
31. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. *Clin Liver Dis*. Feb 2003;7(1):179-194. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12691466.
32. Ledipasvir/sofobuvir (Harvoni) [package insert]. Gilead. 2016. Available at https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf. Accessed July 6, 2016.
33. Daclatasvir (Daklinza) [package insert] Bristol Myers Squibb. 2016. Available at http://packageinserts.bms.com/pi/pi_daklinza.pdf. Accessed July 6, 2016.
34. Elbasavir/grazoprevir (Zapatier) [package insert]. 2016. Available at https://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Accessed July 6, 2016.
35. Ombitasvir/paritaprevir/ritonavir (Technivie) [package insert]. AbbVie. 2016. Available at http://www.rxabbvie.com/pdf/technivie_pi.pdf. Available at July 6, 2016.
36. Ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira) [package insert]. Food and Drug Administration. 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf. Accessed July 6, 2016.

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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 HIV-infected individuals 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 18 through 19e to assess the potential for interactions among different antiretroviral (ARV) drugs and the rifamycins **(BIII)**.

• All HIV-infected patients with active TB who are not on ART should be started on ART as described below:
  • **In patients with CD4 counts <50 cells/mm³:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.
  • **In patients with CD4 counts ≥50 cells/mm³:** Initiate ART within 8 weeks of starting TB treatment **(AIII)**.
  • **In all HIV-infected pregnant women:** 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 HIV-infected patients with active TB, unless precluded because of TB resistance or toxicity. However, rifamycins have a considerable potential for drug-drug interactions. Clinicians should review Tables 18 through 19e to assess the potential for interactions among different ARV drugs and the rifamycins **(BIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Management of Latent Tuberculosis Infection in HIV-Infected Patients

According to the World Health Organization (WHO), approximately one-third of the world's population is infected with tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.[1] HIV-infected persons who are coinfected with TB have a much higher risk of developing active TB than HIV-negative individuals, 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 HIV-infected persons, especially those with a positive tuberculin skin test.[3] After active TB disease has been excluded, the 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 HIV-infected patients who were not on ART.[4] There was no difference in TB incidence in 1,148 South African HIV-infected adults who were

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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 18 through 19e).

If an HIV-infected patient is a contact of an individual infected 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 HIV-infected participants who did not meet WHO criteria for ART initiation to 1 of 4 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 HIV-Infected Patients with Active Tuberculosis

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients 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 HIV-infected patients.

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.

Patients Diagnosed with Tuberculosis While 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 18 through 19e for dosing recommendations).

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Patients 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 HIV/TB-coinfected patients, 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 3 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 3 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 TB-coinfected patients, 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 coinfected 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 coinfected patients,[16,17] but the optimal timing for initiation of ART is unknown. Management of HIV-infected patients with 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 HIV-infected pregnant women with 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

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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 18 through 19e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly.

As a potent enzyme inducer, rifampin use leads to significant reduction in ARV drug exposure; therefore, use of rifampin is not recommended for patients receiving PIs (boosted or unboosted), EVG, etravirine (ETR), rilpivirine (RPV), or TAF. Increased ARV doses are needed when rifampin is used with DTG, RAL, or MVC. In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.[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 18 through 19e 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 HIV-infected individuals[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

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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)**.

References

1. World Health Organization. *Global Tuberculosis Report 2015*. 2015. Available at http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1.
2. Lawn SD, Harries AD, Williams BG, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis*. May 2011;15(5):571-581. Available at http://www.ncbi.nlm.nih.gov/pubmed/21756508.
3. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at http://www.ncbi.nlm.nih.gov/pubmed/20091503.
4. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of M. tuberculosis infection in HIV co-infected persons. *AIDS*. Mar 17 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26990624.
5. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. Jul 7 2011;365(1):11-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/21732833.
6. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine Once-Weekly Dosing Effect on Efavirenz Emtricitabine and Tenofovir PKs. 21st Conference on Retroviruses and Opportunistic Infections; 2014; Boston, MA.
7. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. Apr 2014;69(4):1079-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/24343893.
8. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.
9. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. Aug 27 2015;373(9):795-807. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.
10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed June 22, 2016.
11. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20181971.
12. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. Oct 20 2011;365(16):1492-1501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010915.
13. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1471-1481. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010913.
14. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. Oct 20 2011;365(16):1482-1491. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010914.
15. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. Jan 1 2010;181(1):80-86. Available at

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19833824.

16. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet*. May 22 2010;375(9728):1798-1807. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20488525.
17. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. Apr 5 2014;383(9924):1230-1239. Available at http://www.ncbi.nlm.nih.gov/pubmed/24439237.
18. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. Jun 2011;52(11):1374-1383. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21596680.
19. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
20. Gilead Sciences. *Descovy Product Label*. Foster City, CA. 2016. Available at http://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en.
21. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41(9):681-690. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126459.
22. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. Aug 2013;57(4):586-593. Available at http://www.ncbi.nlm.nih.gov/pubmed/23592830.
23. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother*. Dec 2006;58(6):1299-1302. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17032686.
24. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. Jan 2 2006;20(1):131-132. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327334.
25. Bristol-Myers Squibb. *Sustiva Product Label*. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021360s024lbl.pdf.
26. Centers for Disease C, Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. Dec 9 2011;60(48):1650-1653. Available at http://www.ncbi.nlm.nih.gov/pubmed/22157884.
27. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. May 2012;91(5):881-888. Available at http://www.ncbi.nlm.nih.gov/pubmed/22472995.
28. Podany AT, Bao Y, Swindells S, et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. *Clin Infect Dis*. Oct 15 2015;61(8):1322-1327. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082504.
29. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. Aug 2008;8(8):516-523. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18652998.
30. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Jan 2 2010;24(1):103-108. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19926965.
31. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15918332.
32. Colebunders R, John L, Huyst V, Kambugu A, Scano F, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis*. Sep 2006;10(9):946-953. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16964782.

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33. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. Jan 30 2007;21(3):335-341. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17255740.
34. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Sep 24 2010;24(15):2381-2390. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20808204.

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Limitations to Treatment Safety and Efficacy

Adherence to Antiretroviral Therapy (Last updated May 1, 2014; last reviewed May 1, 2014)

Strict adherence to antiretroviral therapy (ART) is key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival,[1,2] as well as decreased risk of HIV transmission.[3] Conversely, poor adherence is the major cause of therapeutic failure. Achieving adherence to ART is a critical determinant of long-term outcome in HIV infected patients. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV infection, however, loss of virologic control as a consequence of non-adherence to ART may lead to emergence of drug resistance and loss of future treatment options. Many patients initiating ART or already on therapy are able to maintain consistent levels of adherence with resultant viral suppression, CD4+ T-lymphocyte (CD4) count recovery, and improved clinical outcomes. Others, however, have poor adherence from the outset of ART and/or experience periodic lapses in adherence over the lifelong course of treatment. Identifying those with adherence-related challenges that require attention and implementing appropriate strategies to enhance adherence are essential roles for all members of the treatment team.

Recent data underscore the importance of conceptualizing treatment adherence broadly to include early engagement in care and sustained retention in care. The concept of an HIV "treatment cascade" has been used to describe the process of HIV testing, linkage to care, initiation of effective ART, adherence to treatment, and retention in care. The U.S. Centers for Disease Control and Prevention estimates that only 36% of the people living with HIV in the United States are prescribed ART and that among these individuals, only 76% have suppressed viral loads.[4] Thus, to achieve optimal clinical outcomes and to realize the potential public health benefit of treatment as prevention, attention to each step in the treatment cascade is critical.[5] Therefore, provider skill and involvement to retain patients in care and help them achieve high levels of medication adherence are crucial.

This section provides updated guidance on assessing and monitoring adherence and outlines strategies to help patients maintain high levels of adherence.

Factors Associated with Adherence Success and Failure

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.[6] It is critical that each patient receives and understands information about HIV disease including the goals of therapy (achieving and maintaining viral suppression, decreasing HIV-associated morbidity and mortality, and preventing sexual transmission of HIV), the prescribed regimen (including dosing schedule and potential side effects), the importance of strict adherence to ART, and the potential for the development of drug resistance as a consequence of suboptimal adherence. However, information alone is not sufficent to assure high levels of adherence; patients must also be positively motivated to initiate and maintain therapy.

From a patient perspective, nonadherence 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, high levels of alcohol consumption and active substance use, homelessness, poverty, nondisclosure of HIV serostatus, denial, stigma, and inconsistent access to medications).[7-9] Furthermore, patient age may affect adherence. For example, some adolescent and young adult HIV patients, in particular, have substantial challenges in achieving levels of adherence necessary for successful therapeutic outcomes (see HIV-Infected Adolescents section).[10,11] In additon, failure to adopt practices that facilitate adherence, such as linking medication taking to daily activities or using a medication reminder system or a pill organizer, is also associated with treatment failure.[12]

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Characteristics of one or more components of the prescribed regimen can affect adherence. Simple, once-daily regimens,[13] including those with low pill burden, without a food requirement, and few side effects or toxicities, are associated with higher levels of adherence.[14,15] Many currently available ARV regimens are much easier to take and better tolerated than older regimens. Studies have shown that patients taking once-daily regimens have higher rates of adherence than those taking twice-daily dosing regimens.[15] However, data to support or refute the superiority of fixed-dose combination product of 1-pill versus 3-pills (of individual drug products), once-daily regimens—as might be required for the use of some soon-to-be-available generic-based ARV regimens—are limited.

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., with case managers, pharmacists, social workers, psychiatric care providers) are often more successful in supporting patients' complex needs, including their medication adherence-related needs. Further, specific settings, such as prisons and other institutional settings, may thwart or support medication adherence. Drug abuse treatment programs are often best suited to address substance use that may confound adherence and may offer services, such as directly observed therapy, that promote adherence.

Finally, a patient-provider relationship that enhances patient trust through non-judgmental and supportive care and use of motivational strategies can positively influence medication adherence.

Routine Monitoring of Adherence and Retention in Care

Although there is no gold standard for assessing adherence,[1] properly implemented validated tools and assessment strategies can prove valuable in most clinical settings. Viral load suppression is one of the most reliable indicators of adherence and can be used as positive reinforcement to encourage continuous adherence. When patients initiating ART fail to achieve viral suppression by 24 weeks of treatment, the possibility of suboptimal adherence and other factors must be assessed. Similarly, treatment failure as measured by detectable viral load during chronic care is most likely the result of non-adherence. Patient self-report, the most frequently used method for evaluating medication adherence, remains a useful tool for assessing adherence over time. However, self-reports must be properly and carefully assessed as patients may overestimate adherence. While carefully assessed patient self report of high-level adherence to ART has been associated with favorable viral load responses,[16,17] patient admission of suboptimal adherence is highly correlated with poor therapeutic response. The reliability of self report often depends on how the clinican 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 or "white coat adherence" responses. Some patients may selectively adhere to components of a regimen believed to have the fewest side effects or the lowest dosing frequency or pill burden. To allow patients to more accurately disclose lapses in adherence, some experts suggest that providers inquire about the number of missed doses during a defined time period rather than directly asking "Are you taking your medicines?" Others advocate simply asking patients to rate their adherence during the last 4 weeks on a 5- or 6-point Likert scale.[18,19] Regardless of how obtained, patient self-report, in contrast to other measures of adherence, allows for immediate patient-provider discussion to identify reasons for missed doses and to explore corrective strategies.

Other measures of adherence include pharmacy records and pill counts. Pharmacy records can be valuable when medications are obtained exclusively from a single source so that refills can be traced. Pill counts are commonly used but can be altered by patients. Other methods of assessing adherence include the use of therapeutic drug monitoring and electronic measurement devices (e.g., MEMS bottle caps and dispensing systems). However, these methods are costly and are usually done primarily in research settings.

Interventions to Improve Adherence and Retention in Care

A continuum of ART adherence support services is necessary to meet individual patient needs. All health care

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team members, including physicians, physician assistants, nurse practitioners, nurse midwives, nurses, pharmacists, medication managers, and social workers play integral roles in successful adherence programs.[17,20-22]

Effective adherence interventions vary in modality and duration, and by clinical setting, provider, and patient. There are many options that can be customized to suit a range of needs and settings (see Table 13). An increasing number of interventions have proven effective in improving adherence to ART. For descriptions of the interventions, see: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm.[23]

Clinicians should provide all patients with a basic level of adherence-related information and support. Before writing the first prescription(s) for patients initiating or reinitiating ART, clinicians should assess the patient's adherence readiness. Clinicians should evaluate patients' knowledge about HIV disease, treatment, and prevention and provide basic information about ART, viral load and CD4 count and the expected outcome of ART based on these parameters, the importance of strict adherence to ART, and the consequences of non-adherence. In addition, clinicians should assess patients' motivation to successfully adhere to ART and identify and support facilitating factors and address potential barriers to adherence. Finally, clinicians should be assured that patients have the necessary medication taking skills to follow the regimen as prescribed.

Given the wide array of treatment options, individualizing treatment with patient involvement in decision making is the cornerstone of treatment planning and therapeutic success. The first principle of successful treatment is to design an understandable plan to which the patient can commit.[24,25] It is important to consider the patient's daily schedule; patient 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/her routine daily activities. If necessary, soliciting help from family members may also improve adherence. Patients who are naive to ART should understand that their first regimen usually offers the best chance for taking a simple regimen that affords long-term treatment success and prevention of drug resistance. Establishing a trusting patient-provider relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. Medication taking can also be enhanced by the use of pill organizers and medication reminder aids (e.g., alarm clock, pager, calendar).

Positive reinforcement can greatly help patients maintain high levels of adherence. This technique to foster adherence includes informing patients of their low or suppressed HIV viral load levels and increases in CD4 cell counts. Motivational interviewing has also been used with some successes. Recognizing high levels of adherence with incentives and rewards can facilitate treatment success in some patients. Adherence-contingent reward incentives such as meal tickets, grocery bags, lotto tickets, and cash have been used in the treatment of HIV and other chronic diseases. The effectiveness of using cash incentives to promote HIV testing, entry to care, and adherence to ART is currently being studied in the multi-site HPTN 065 trial. Other effective interventions include nurse home visits, a five-session group intervention, pager messaging, and couples or family-based interventions. To maintain high levels of adherence in some patients, it is critically important to provide substance abuse therapy and to strengthen social support. Directly observed therapy (DOT) has been effective in providing ART to active drug users[26] but not to patients in a general clinic population.[27]

To determine whether additional adherence or retention interventions are warranted, assessments should be done at each clinical encounter and should be the responsibility of the entire health care team. Routine monitoring of HIV viral load, pharmacy records, and indicators that measure retention in care are useful to determine if more intense efforts are needed to improve adherence. Patients with a history of non-adherence to ART are at risk for poor adherence when re-starting therapy with the same or new drugs. Special attention should be given to identify and address any reason for previous poor adherence. Preferential use of ritonavir-boosted protease inhibitor-(PI/r)-based ART, which has a higher barrier to the development of resistance than

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other treatment options, should be considered if poor adherence is predicted.

The critical elements of adherence go hand in hand with linkage-to-care and retention in care. A recently released guideline provides a number of strategies to improve entry and retention in care and adherence to therapy for HIV infected patients.[5] As with adherence monitoring, research advances offer many options for systematic monitoring of retention in care that may be used in accordance with local resources and standards. The options include surveillance of visit adherence, gaps in care, and the number of visits during a specified period of time.[28]

Conclusion

Adherence to ART is central to therapeutic success. Given the many available assessment strategies and interventions, the challenge for the treatment team is to select the techniques that best fit each patient and patient population, and, according to available resources, the treatment setting. In addition to maintaining high levels of medication adherence, attention to effective linkage to care, engagement in care, and retention in care is critical for successful treatment outcomes. To foster treatment success, there are interventions to support each step in the cascade of care, as well as guidance on systematic monitoring of each step in the cascade.[5]

Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
(page 1 of 3)

Strategies	Examples
Use a multidisciplinary team approach. Provide an accessible, trustworthy health care team.	• Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers
Strengthen early linkage to care and retention in care.	• Encourage healthcare team participation in linkage to and retention in care.
Assess patient readiness to start ART.	
Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information.	• Considering the patient's current knowledge base, 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, and therapeutic and prevention consequences of non-adherence.
Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication.	• Assess patient's cognitive competence and impairment. • Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure 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 non-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.
Provide needed resources.	• Provide or refer for mental health and/or substance abuse treatment. • Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security.

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Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Involve the patient in ARV regimen selection.	• Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence. • Assess daily activities and tailor regimen to predictable and routine daily events. • Consider preferential use of PI/r-based ART if poor adherence is predicted. • Consider use of fixed-dose combination formulation. • Assess if cost/co-payment for drugs can affect access to medications and adherence.
Assess adherence at every clinic visit.	• Monitor viral load as a strong biologic measure of adherence. • Use a simple behavioral rating scale. • 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 adherence.
Use positive reinforcement to foster adherence success.	• Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts. • When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success.
Identify the type of and reasons for nonadherence.	• Failure to fill the prescription(s) • Failure to understand dosing instructions • Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements) • Pill aversion • Pill fatigue • Adverse effects • Inadequate understanding of drug resistance and its relationship to adherence • Cost-related issues • Depression, drug and alcohol use, homelessness, poverty • Stigma • Non-disclosure • Other potential barriers
Select from among available effective treatment adherence interventions.	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. • Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices). • Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates). • Use patient prescription assistance programs. • Use motivational interviews.

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Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care
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Strategies	Examples
Systematically monitor retention in care.	• Record and follow up on missed visits.
On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available.	• Provide outreach for those patients who drop out of care. • Use peer or paraprofessional treatment navigators. • Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence. • Arrange for directly observed therapy (if feasible).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor

References

1. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune Defic Syndr*. 2006;43 Suppl 1:S149-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/17133199.
2. World Heath Organization (WHO). Adherence to long term therapies—evidence for action. 2003. Available at http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/pubmed/21767103.
4. Centers for Disease Control and Prevention. *Linkage to and retention in HIV Medical Care*. 2012. Available at http://www.cdc.gov/hiv/prevention/programs/pwp/linkage.html. Accessed on January 20, 2014.
5. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med*. 2012;156(11):817-833. Available at http://www.ncbi.nlm.nih.gov/pubmed/22393036.
6. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med*. 2004;19(11):1096-1103. Available at http://www.ncbi.nlm.nih.gov/pubmed/15566438.
7. Halkitis PN, Shrem MT, Zade DD, Wilton L. The physical, emotional and interpersonal impact of HAART: exploring the realities of HIV seropositive individuals on combination therapy. *J Health Psychol*. 2005;10(3):345-358. Available at http://www.ncbi.nlm.nih.gov/pubmed/15857867.
8. Stirratt MJ, Remien RH, Smith A, et al. The role of HIV serostatus disclosure in antiretroviral medication adherence. *AIDS Behav*. 2006;10(5):483-493. Available at http://www.ncbi.nlm.nih.gov/pubmed/16721505.
9. Carr RL, Gramling LF. Stigma: a health barrier for women with HIV/AIDS. *J Assoc Nurses AIDS Care*. 2004;15(5):30-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/15358923.
10. Ryscavage P, Anderson EJ, Sutton SH, Reddy S, Taiwo B. Clinical outcomes of adolescents and young adults in adult HIV care. *J Acquir Immune Defic Syndr*. 2011;58(2):193-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/21826014.
11. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. 2009;23(3):185-194. Available at http://www.ncbi.nlm.nih.gov/pubmed/19866536.
12. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychol*. 2006;25(4):462-473. Available at http://www.ncbi.nlm.nih.gov/pubmed/16846321.
13. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*. 2009;48(4):484-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/19140758.
14. Raboud J, Li M, Walmsley S, et al. Once daily dosing improves adherence to antiretroviral therapy. *AIDS Behav*. 2011;15(7):1397-1409. Available at http://www.ncbi.nlm.nih.gov/pubmed/20878227.
15. Nachega JB, Parienti JJ, Uthman OA, et al. Lower Pill Burden and Once-daily Dosing Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. *Clin Infect Dis*. 2014. Available at

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http://www.ncbi.nlm.nih.gov/pubmed/24457345.

16. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10(3):227-245. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16783535.
17. Mannheimer SB, Morse E, Matts JP, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. *J Acquir Immune Defic Syndr*. 2006;43 Suppl 1:S41-47. Available at http://www.ncbi.nlm.nih.gov/pubmed/17091022.
18. Feldman BJ, Fredericksen RJ, Crane PK, et al. Evaluation of the single-item self-rating adherence scale for use in routine clinical care of people living with HIV. *AIDS Behav*. 2013;17(1):307-318. Available at http://www.ncbi.nlm.nih.gov/pubmed/23108721.
19. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav*. 2008;12(1):86-94. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17577653.
20. McPherson-Baker S, Malow RM, Penedo F, Jones DL, Schneiderman N, Klimas NG. Enhancing adherence to combination antiretroviral therapy in non-adherent HIV-positive men. *AIDS Care*. 2000;12(4):399-404. Available at http://www.ncbi.nlm.nih.gov/pubmed/11091772.
21. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. *J Assoc Nurses AIDS Care*. 2005;16(5):3-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/16433105.
22. Remien RH, Stirratt MJ, Dognin J, Day E, El-Bassel N, Warne P. Moving from theory to research to practice. Implementing an effective dyadic intervention to improve antiretroviral adherence for clinic patients. *J Acquir Immune Defic Syndr*. 2006;43 Suppl 1:S69-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17133206.
23. Centers for Disease Control and Prevention. Compendium of Evidence-Based HIV Behavioral Interventions: Medication Adherence Chapter. 2011. Available at http://www.cdc.gov/hiv/topics/research/prs/ma-chapter.htm.
24. Williams A, Friedland G. Adherence, compliance, and HAART. *AIDS Clin Care*. 1997;9(7):51-54, 58. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11364415&dopt=Abstract.
25. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001;26(5):331-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/11679023.
26. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis*. 2007;45(6):770-778. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17712763.
27. Berg KM, Litwin AH, Li X, Heo M, Arnsten JH. Lack of sustained improvement in adherence or viral load following a directly observed antiretroviral therapy intervention. *Clin Infect Dis*. 2011;53(9):936-943. Available at http://www.ncbi.nlm.nih.gov/pubmed/21890753.
28. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. *AIDS Patient Care STDS*. 2010;24(10):607-613. Available at http://www.ncbi.nlm.nih.gov/pubmed/20858055.

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Adverse Effects of Antiretroviral Agents (Last updated July 14, 2016; last reviewed July 14, 2016)

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects of some antiretroviral (ARV) drugs. However, adverse effects have been reported with the use of all antiretroviral (ARV) drugs and, in the earlier era of combination ART, 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 have treatment-limiting adverse events. However, the longer-term complications of ART can be underestimated because most clinical trials enroll a select group of patients based on highly specific inclusion criteria and the duration of participant follow-up is relatively short. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and therapy has to 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 such as bone or renal toxicity, dyslipidemia, insulin resistance, or accelerated cardiovascular disease. 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 (eg, alcoholism or coinfection with viral hepatitis[2,3] may increase the risk of hepatotoxicity; psychiatric disorders may be exacerbated by efavirenz [EFV]- and, infrequently, by integrase strand transfer inhibitor [INSTI]-related CNS toxicities;[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,[8] and atazanavir (ATV)-associated hyperbilirubinemia.[9]

Information on the adverse effects of ARVs is outlined in several tables in the guidelines. Table 14 provides clinicians with a list of the most common and/or severe known ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 1–6.

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

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

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia. **TPV:** Intracranial hemorrhage associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, vitamin E	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:** Smaller declines in BMD than 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
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.	**RPV:** QTc prolongation	Associated with MI and stroke in some cohorts. **SQV/r, ATV/r, and LPV/r:** PR prolongation (risks include pre-existing heart disease, other medications). **SQV/r:** QT prolongation. Obtain ECG before administering SQV.	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
Diabetes Mellitus/ Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all PIs	N/A	N/A

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Dyslipidemia	**d4T > ZDV > ABC:** ↑TG and LDL **TAF > TDF:** ↑TG, ↑LDL, ↑HDL (no change in TC:HDL ratio)	**EFV:** ↑TG, ↑LDL, ↑HDL	**All RTV- or COBI-boosted PIs:** ↑TG, ↑LDL, ↑HDL **LPV/r = FPV/r and LPV/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 (eg, diarrhea, nausea, vomiting) **Common with LPV/r and more frequent than with DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A
Hepatic Effects	Reported with most NRTIs. **ZDV, d4T, or ddI:** Steatosis most common **ddI:** Prolonged exposure linked to noncirrhotic portal hypertension, esophageal varices. **When TAF, TDF, 3TC, and FTC are withdrawn or when HBV resistance develops:** HIV/HBV-coinfected patients may develop severe hepatic flares.	NVP > other NNRTIs **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. NVP should **never** be used for postexposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency with TPV/r. **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia **TPV/r: Contraindicated** in patients with hepatic insufficiency (Child-Pugh B or C)	N/A	**MVC:** Hepatotoxicity with or without rash or HSRs reported

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if HLA-B*5701 positive. Median onset 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, regardless of HLA-B*5701 status, should not be rechallenged with ABC if HSR is suspected.	**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 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall, risk is higher for women than men. Two-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL given in combination with other drugs known to cause HSR. All ARVs should be stopped if HSR occurs. **DTG:** Reported in <1% of patients in clinical development program	**MVC:** 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

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	**Lipoatrophy:** d4T > ZDV. May be more likely when NRTIs combined with EFV than with an RTV-boosted PI.	Lipohypertophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated Creatine Phosphokinase	**ZDV:** Myopathy	N/A	N/A	**RAL:** ↑CPK, weakness and rhabdomyolysis	N/A
Nervous System/ Psychiatric Effects	**d4T > ddI and ddC:** Peripheral neuropathy: (can be irreversible). **d4T:** Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare).	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2 to 4 weeks. Bedtime dosing may reduce symptoms. Risks include 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 (especially among younger patients and those with history of mental illness or substance abuse) was found in a retrospective analysis of comparative trials. **RPV:** Depression, suicidality, sleep disturbances	N/A	**All INSTIs:** Insomnia, depression, and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	**FTC:** Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, TPV	RAL, EVG	MVC

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Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Renal Effects/ Urolithiasis	**TDF:** ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, 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.	N/A	**ATV and LPV/r:** Increased risk of chronic kidney disease in a large cohort study. **IDV:** ↑SCr, pyuria, renal atrophy or hydronephrosis **IDV, ATV:** Stone, crystal formation; adequate hydration may reduce risk.	**COBI and DTG:** Inhibits Cr secretion without reducing renal glomerular function.	N/A
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	**ddI, ZDV:** Reported cases	NVP > DLV, EFV, ETR, RPV	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	RAL	N/A

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CrCl = creatinine clearance; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; 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; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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Switching Antiretroviral Therapy Because of Adverse Effects

Some patients experience treatment-limiting ART-associated toxicities, and 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 (eg, 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 (eg, urolithiasis with atazanavir [ATV], renal tubulopathy with tenofovir disoproxil fumarate [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 (eg, 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 selected for, regardless of whether previously or currently identified by genotypic resistance testing, are archived in HIV reservoirs. Even if resistance mutations are absent from subsequent resistance test results, they may reappear under selective pressure. It is critical that providers review the following 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 maraviroc [MVC] is being considered);
- HLA-B*5701 status (if ABC is being considered);
- Comorbidities;
- Adherence history;
- Prior intolerances to any ARVs; and
- Concomitant medications and supplements for potential drug interactions with ARVs.

A patient's acceptance of new food or dosing requirements must also be assessed. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of ART-associated adverse events may mimic those of comorbidities, adverse effects of concomitant medications, or HIV infection. Therefore, concurrent with ascribing a particular clinical event to ART, alternative causes for the event should be investigated. 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 15 lists several major ART-associated adverse events and potential options to appropriately switch 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, findings of comparative ARV trials and observational cohort studies, or expert opinion. Switching a successful ARV regimen should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.

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Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 2)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Bone Density Effects	TDF[a]	ABC[b] or TAF NRTI-sparing regimens or regimens using only 3TC or FTC as 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 with improvement in BMD upon switching from TDF. 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.
Central Nervous System, Neuropsychiatric Side Effects Dizziness, suicidal ideation, abnormal dreams, depression	EFV, RPV	ETR or a PI/c or PI/r INSTIs may be considered (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; EFV; EVG/c	RAL, DTG, RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Gastrointestinal Effects Nausea, diarrhea	LPV/r	ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, 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 persistent and intolerable.
	Other RTV- or COBI-boosted regimens	RAL, DTG, 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 MVC	Non-INSTI ART Suitable alternative ART	Reactions to NVP, ETR, RAL, DTG and MVC may be accompanied by elevated liver transaminases.
Insulin Resistance	LPV/r, FPV/r	INSTI, RPV	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 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.

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Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 2)

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Lipoatrophy Subcutaneous fat wasting of limbs, face, buttocks	d4T, ZDV	TDF, TAF, or ABC[b]	Peripheral lipoatrophy is a legacy of 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, dorso-cervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (eg, 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 developing 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 (eg, INSTI)	Mild rashes following DRV/r use may resolve with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.
Renal Effects Including proximal renal tubulopathy, elevated creatinine	TDF[a]	ABC[b] or TAF (for patients with CrCl >30mL/min) or NRTI-sparing regimens, or regimens using only 3TC or FTC as 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, RAL, or NNRTI	COBI and DTG, and to a lesser extent RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess 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	Assuming that ATV is believed to be causing the stones.

[a] In patients with chronic active HBV infection, another agent 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 co-administered with TDF. Long-term data for unboosted ATV are unavailable.

Key to Abbreviations: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CNS = central nervous system; COBI or c = cobicistat; d4T = stavudine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; 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; 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; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr*. 2003;34(4):407-414. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14615659.
2. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. Dec 22 2000;14(18):2895-2902. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153671.
3. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob Agents Chemother*. Dec 2000;44(12):3451-3455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11083658.
4. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. Sep 12 2008;22(14):1890-1892. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753871.
5. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. Aug 24 2015;29(13):1723-1725. Available at http://www.ncbi.nlm.nih.gov/pubmed/26372287.
6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18256392.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18444831.
8. Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010;7:32. Available at http://www.ncbi.nlm.nih.gov/pubmed/20723261.
9. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS*. Jan 2 2007;21(1):41-46. Available at http://www.ncbi.nlm.nih.gov/pubmed/17148966.

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

Costs as They Relate to Adherence from a Patient Perspective

Cost sharing: Cost sharing is where the patient is responsible for some of the medication cost burden (usually accomplished via co-payments, co-insurance, 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, co-payment 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 co-pays 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 non-adherence.[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 co-formulation 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 co-formulated 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 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 the Laboratory Monitoring section). 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

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greater scale. One analysis suggests the possibility of saving approximately $900 million nationally in the first year of switching from a branded fixed-dose combination product to a three-pill regimen containing generic efavirenz.[3]

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

Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir				
• Generic	300 mg tablet	2 tablets daily	60 tablets	$602.66
• Ziagen	300 mg tablet	2 tablets daily	60 tablets	$670.37
• Ziagen	20 mg/mL solution	30 mL daily	900 mL	$660.86
Emtricitabine				
• Emtriva	200 mg capsules	1 capsule daily	30 capsules	$643.82
• Emtriva	10 mg/mL solution	24 mL daily	680 mL (28-day supply)	$643.82
Lamivudine				
• Generic	300 mg tablet	1 tablet daily	30 tablets	$283.89
• Epivir	300 mg tablet	1 tablet daily	30 tablets	$498.89
• Epivir	10 mg/mL solution	30 mL daily	900 mL	$498.90
Tenofovir Disoproxil Fumarate				
• Viread	300 mg tablet	1 tablet daily	30 tablets	$1,197.32
Zidovudine				
• Generic	300 mg tablet	1 tablet twice daily	60 tablets	$54.00–$360.97
NRTI Combination Products				
Abacavir/Lamivudine				
• Epzicom	600/300 mg tablets	1 tablet daily	30 tablets	$1,550.05
Tenofovir Alafenamide /Emtricitabine				
• Descovy	25/200 mg tablet	1 tablet daily	30 tablets	$1,759,73
Tenofovir Disoproxil Fumarate/Emtricitabine				
• Truvada	300/200 mg tablet	1 tablet daily	30 tablets	$1,759.73

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Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Zidovudine/Lamivudine				
• Generic	300/150 mg tablet	1 tablet twice daily	60 tablets	$877.85
• Combivir	300/150 mg tablet	1 tablet twice daily	60 tablets	$1,081.70
Abacavir Sulfate/Zidovudine/ Lamivudine				
• Generic	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,738.46
• Trizivir	300/300/150 mg tablet	1 tablet twice daily	60 tablets	$1,931.64
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz				
• Sustiva	600 mg tablet	1 tablet daily	30 tablets	$1,010.13
Etravirine				
• Intelence	200 mg tablet	1 tablet twice daily	60 tablets	$1,308.06
Nevirapine				
• Generic	200 mg tablet	1 tablet twice daily	60 tablets	$648.19
• Viramune	200 mg tablet	1 tablet twice daily	60 tablets	$912.86
• Viramune XR	400 mg tablet	1 tablet daily	30 tablets	$846.66
Rilpivirine				
• Edurant	25 mg tablet	1 tablet daily	30 tablets	$1,075.15
Protease Inhibitors (PIs)				
Atazanavir				
• Reyataz	200 mg capsule	2 capsules daily	60 capsules	$1,656.52
• Reyataz	300 mg capsule[d]	1 capsule daily	30 capsules	$1,640.86
Atazanavir/Cobicistat				
• Evotaz	300/150 mg tablet	1 tablet daily	30 tablets	$1,817.51
Darunavir				
• Prezista	600 mg tablet[e]	1 tablet twice daily	60 tablets	$1,629.06
• Prezista	800 mg tablet[d]	1 tablet daily	30 tablets	$1,629.06
• Prezista	100 mg/mL suspension[e]	8 mL daily 6 mL twice daily	240 mL 360 mL	$1,086.05 $1,629.07
Darunavir/Cobicistat • Prezcobix	800/150 mg tablet	1 tablet daily	30 tablets	$1,862.12
Lopinavir/Ritonavir • Kaletra	200/50 mg tablet	2 tablets twice daily or 4 tablets once daily	120 tablets	$1,106.29
• Kaletra	80/20 mg per mL solution	5 mL twice daily	300 mL	$1,037.14
Tipranavir • Aptivus	250 mg capsule[e]	2 capsules twice daily	120 capsules	$1,685.59

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Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)
Integrase Strand Transfer Inhibitors (INSTIs)				
Dolutegravir • Tivicay	50 mg tablet	1 tablet once daily	30 tablets	$1,707.26
• Tivicay	50 mg tablet	1 tablet twice daily	60 tablets	$3,414.52
Elvitegravir • Vitekta	85 mg tablet	1 tablet daily	30 tablets	$1,445.34
• Vitekta	150 mg tablet	1 tablet daily	30 tablets	$1,445.34
Raltegravir • Isentress	400 mg tablet	1 tablet twice daily	60 tablets	$1,545.07
Fusion Inhibitor				
Enfuviritide • Fuzeon	90 mg injection kit	1 injection twice daily	60 doses (1 kit)	$4,097.78
CCR5 Antagonist				
Maraviroc • Selzentry	150 mg tablet	1 tablet twice daily	60 tablets	$1,296.77
• Selzentry	300 mg tablet	1 tablet twice daily	60 tablets	$1,296.77
• Selzentry	300 mg tablet	2 tablets twice daily	120 tablets	$2,593.54
Co-Formulated Combination Products as Single Tablet Regimens				
Dolutegravir/Abacavir/Lamivudine • Triumeq	50/600/300 mg tablet	1 tablet daily	30 tablets	$2,889.22
Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine • Atripla	600/300/200 mg tablet	1 tablet daily	30 tablets	$2,869.86
Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine • Genvoya	150/150/10/200 mg tablet	1 tablet daily	30 tablets	$3,093.19
Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine • Stribild	150/150/300/200 mg tablet	1 tablet daily	30 tablets	$3,244.76
Rilpivirine/Tenofovir Alafenamide/Emtricitabine • Odefsey	25/25/200 mg tablet	1 tablet daily	30 tablets	$2,815.04
Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine • Complera	25/300/200 mg tablet	1 tablet daily	30 tablets	$2,815.04
Pharmacokinetic Enhancers (Boosters)				
Cobicistat • Tybost	150 mg tablet	1 tablet daily	30 tablets	$230.90
Ritonavir: Total daily dose depends on the dose of the concomitant PI (100 mg once or twice daily, or 200 mg twice daily) • Norvir	100 mg tablet	1 tablet once daily	30 tablets	$308.60
	80 mg/mL solution	100 mg daily	37.5 mL (of a 240 mL bottle)	$270.04

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Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)

ARV Drug (Generic and Brand Names)	Strength Formulation	Dosing	Tablets, Capsules, or mLs per Month[a]	AWP[b] (Monthly)

[a] Represents 30 days or as specified.

[b] AWP = average wholesale price. Note that the AWP may not represent the pharmacy acquisition price or the price paid by consumers.

Source: http://micromedexsolutions.com. Accessed April 2016.

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

[d] Should be used in combination with ritonavir or cobicistat. Please refer to Appendix B, Table 3 for ritonavir doses.

[e] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Abbreviations: ARV = antiretroviral; EC = enteric coated; XR = extended release

References

1. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001;344(11):824-831. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11248160.
2. Mauskopf J, Brogan AJ, Talbird SE, Martin S. Cost-effectiveness of combination therapy with etravirine in treatment-experienced adults with HIV-1 infection. *AIDS*. 2012;26(3):355-364. Available at http://www.ncbi.nlm.nih.gov/pubmed/22089378.
3. Walensky RP, Sax PE, Nakamura YM, et al. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med*. 2013;158(2):84-92. Available at http://www.ncbi.nlm.nih.gov/pubmed/23318310.
4. Bayoumi AM, Barnett PG, Joyce VR, et al. Cost-effectiveness of newer antiretroviral drugs in treatment-experienced patients with multidrug-resistant HIV disease. *J Acquir Immune Defic Syndr*. 2013;64(4):382-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/24129369.
5. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*. 2007;298(1):61-69. Available at http://www.ncbi.nlm.nih.gov/pubmed/17609491.
6. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment reductions generate greater medication adherence in targeted patients. *Health Affair*. 2010;29(11):2002-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21041739.
7. Abdelgawad T, Egbuonu-Davis L. Preferred drug lists and Medicaid prescriptions. *PharmacoEconomics*. 2006;24 Suppl 3:55-63. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266388.
8. Ridley DB, Axelsen KJ. Impact of Medicaid preferred drug lists on therapeutic adherence. *PharmacoEconomics*. 2006;24 Suppl 3:65-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17266389.
9. Wilson J, Axelsen K, Tang S. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. *Am J Manag Care*. 2005;11 Spec No:SP27-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/15700907.
10. Raper JL, Willig JH, Lin HY, et al. Uncompensated medical provider costs associated with prior authorization for prescription medications in an HIV clinic. *Clin Infect Dis*. 2010;51(6):718-724. Available at http://www.ncbi.nlm.nih.gov/pubmed/20695800.
11. Hanna DB, Hessol NA, Golub ET, et al. Increase in Single-Tablet Regimen Use and Associated Improvements in Adherence-Related Outcomes in Hiv-Infected Women. *J Acquir Immune Defic Syndr*. 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/24326606.
12. Nachega JB, Parienti JJ, Uthman OA, et al. Lower Pill Burden and Once-daily Dosing Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. *Clin Infect Dis*. 2014. Available at http://www.ncbi.nlm.nih.gov/pubmed/24457345.

Downloaded from http://aidsinfo.nih.gov/guidelines on 1/31/2017

13. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4 testing in patients with HIV-1 RNA suppression on antiretroviral treatment? Analysis of the ARTEMIS trial. *AIDS*. 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23842127.
14. Hyle EP, Sax PE, Walensky RP. Potential Savings by Reduced CD4 Monitoring in Stable Patients With HIV Receiving Antiretroviral Therapy. *JAMA Intern Med*. 2013. Available at http://www.ncbi.nlm.nih.gov/pubmed/23978894.

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Drug-Drug Interactions (Last updated July 14, 2016; last reviewed July 14, 2016)

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 other drugs a patient is taking. A thorough review of concomitant medications in consultation with a clinician with expertise 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 prescribing interacting drugs is necessary, 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 17.

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 ARVs that require gastric acidity for optimal absorption (ie, atazanavir [ATV] and rilpivirine [RPV]).
- Products that contain polyvalent cations, such as aluminum, calcium, magnesium-containing antacids, supplements, or iron products, can bind to integrase inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme 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.

1. The cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). Cytochrome P450 3A4 (CYP3A4) is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
2. The uridine diphosphate (UDP)-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 agents are potent inhibitors of the CYP3A4 enzyme, resulting in

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higher drug exposures of the coadministered ARV metabolized by this pathway. Importantly, RTV and COBI may 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 anion 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 18-20b provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modifications or alternative therapy.

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 1 of 2)

Pharmacokinetic 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 (eg, transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: Ellipses (…) indicate that there are no clinically relevant interactions by these mechanisms.

ARV Drugs by Drug Class	Mechanisms That May Affect or Be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Integrase Strand Transfer Inhibitors (INSTIs)								
Dolutegravir (DTG)	…	Concentration decreased by products containing polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Substrate	3A4 (small contribution)	…	…	Substrate	Inhibitor of renal transporters OCT2 and MATE
Elvitegravir (EVG)	…		…	3A4	…	2C9	Substrate	…
Raltegravir (RAL)	…		…	…	…	…	Substrate	…
Pharmacokinetic (PK) Enhancers (Boosters)								
Cobicistat (COBI)	…	…	Inhibitor	3A4	3A4, 2D6	…	…	…
Ritonavir (RTV)	…	…	Substrate, inhibitor	3A4, 2D6	3A4, 2D6 (lesser extent)	1A2, 2C8, 2C9, 2C19	Inducer	…
Protease Inhibitors (PIs) **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Atazanavir (ATV)	Concentration decreased	…	Substrate, inducer, inhibitor	3A4	3A4, 2C8 (weak)	…	Inhibitor	OATP inhibitor
Darunavir (DRV)	…	…	Substrate	3A4	3A4	2C9	…	OATP inhibitor

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Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect or be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Protease Inhibitors (PIs), continued **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Fosamprenavir (FPV)	Concentration decreased by H2 antagonist	…	Substrate, inhibitor	3A4	3A4	3A4 (weak)	…	…
Lopinavir (LPV)	…	…	Substrate	3A4	3A4	…	…	OATP inhibitor
Saquinavir (SQV)	…	…	Substrate, inhibitor	3A4	3A4	…	…	OATP inhibitor
Tipranavir (TPV)	…	…	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	…	OATP inhibitor
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)								
Efavirenz (EFV)	…	…	…	2B6 (primary), 2A6, 3A4	2C9, 2C19, 3A4	3A4, 2B6	…	…
Etravirine (ETR)	…	…	Inducer	3A4, 2C9, 2C19	2C9, 2C19	3A4	…	…
Nevirapine (NVP)	…	…	…	3A4, 2B6	…	3A4, 2B6	…	…
Rilpivirine (RPV)	Concentration decreased	…	…	3A4	…	…	…	…
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)								
Abacavir (ABC)	…	…	…	…	…	…	Substrate	Alcohol dehydrogenase substrate
Emtricitabine (FTC)	…	…	…	…	…	…	…	…
Lamivudine (3TC)	…	…	…	…	…	…	…	…
Tenofovir alafenamide (TAF)	…	…	Substrate	…	…	…	…	OATP substrate
Tenofovir disoproxil fumarate (TDF)	…	…	Substrate	…	…	…	…	Competition of active renal tubular secretion
Zidovudine (ZDV)	…	…	…	…	…	…	…	Glucuronidation
CCR5 Antagonist								
Maraviroc (MVC)	…	…	Substrate	3A4	…	…	…	…
Fusion Inhibitor								
Enfuvirtide (T20)	…	…	…	…	…	…	…	…

Key to Abbreviations: Al = aluminium; ARV = antiretroviral; Ca = calcium; CYP = cytochrome P; Fe = iron; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; OATP = organic anion-transporting polypeptide; OCT2 = organic cation transporter 2; UGT1A1 = uridine diphosphate glucuronosyltransferase; Zn = zinc

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Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Anti-infective Agents	Antiepileptic Agents	Neurologic Agents	Herbs	HCV Agents[c]	Other Agents
ATV +/– RTV or COBI	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	**ATV/c only:** Carbamazepine Phenobarbital Phenytoin	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Elbasvir/ Grazoprevir Simeprevir	Alfuzosin Cisapride[f] Ergot derivatives Flibanserin Irinotecan Salmeterol Sildenafil for PAH
DRV/c or DRV/r	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	**DRV/c only:** Carbamazepine Phenobarbital Phenytoin	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
FPV +/– RTV	Dronedarone Eplerenone Flecainide Ivabradine Propafenone Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	None	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
LPV/r	Dronedarone Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin[f] Rifapentine	None	Lurasidone Midazolam[e] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
SQV/r	Amiodarone Disopyramide Dofetilide Dronedarone Eplerenone Flecainide Ivabradine Lidocaine Propafenone Quinidine Ranolazine	Lovastatin Simvastatin	Clarithromycin Dapsone Erythromycin Pentamidine (parenteral) Rifampin[f] Rifapentine Quinine	None	Clozapine Haloperidol Lurasidone Midazolam[e] Phenothiazines[g] Pimozide Trazodone Triazolam Ziprasidone	ments St. John's wort Garlic supple-	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[f] Ergot derivatives Flibanserin Tacrolimus Salmeterol Sildenafil for PAH
TPV/r	Amiodarone Dronedarone Eplerenone Flecainide Ivabradine Propafenone Quinidine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	None	Lurasidone Midazolam[d] Pimozide Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ledipasvir Ombitasvir Paritaprevir Simeprevir Sofosbuvir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
EFV	None	None	None	None	None	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	None

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Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

ARV Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Anti-infective Agents	Antiepileptic Agents	Neurologic Agents	Herbs	HCV Agents[c]	Other Agents
ETR	None	None	Rifampin Rifapentine	Carbamazepine Phenobarbital Phenytoin	None	St John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Clopidogrel
NVP	None	None	Rifapentine	None	None	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ombitasvir Paritaprevir Simeprevir	Ketoconazole
RPV	None	None	Rifampin Rifapentine	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	None	St. John's wort	Dasabuvir Ombitasvir Paritaprevir	Proton pump inhibitors
MVC	None	None	Rifapentine	None	None	St. John's wort	Dasabuvir Ombitasvir Paritaprevir	None
DTG	Dofetilide	None	Rifapentine	None	None	St. John's wort	None	None
EVG/c **For EVG + PI/r, refer to agents listed for the selected PI**	Eplerenone Ivabradine Ranolazine	Lovastatin Simvastatin	Rifampin Rifapentine	Carbamazepine Phenobarbital Phenytoin	Lurasidone Pimozide Midazolam[d] Triazolam	St. John's wort	Dasabuvir Elbasvir/ Grazoprevir Ledipasvir Ombitasvir Paritaprevir Simeprevir	Alfuzosin Cisapride[e] Ergot derivatives Flibanserin Salmeterol Sildenafil for PAH
RAL	None	None	None	None	None	None	None	None
TAF	None	None	Rifabutin Rifampin Rifapentine	None	None	St. John's wort	None	None

a. DLV, IDV, NFV, RTV (as sole PI), T-20, and NRTIs other than TAF are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

b. Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

c. HCV agents listed include only those that are commercially available at the publication of these guidelines.

d. Use of oral midazolam is contraindicated. Single-dose parenteral midazolam can be used with caution and can be given in a monitored situation for procedural sedation.

e. The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

f. In healthy volunteer studies, a high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect; therefore, these dosing strategies should not be used when alternatives exist.

g. Phenothiazines include chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, promethazine, and thioridazine.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 19a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 19a and 19b)

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• **Midazolam, triazolam:** Temazepam, lorazepam, oxazepam

• **Sildenafil for PAH:** Selexipag

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; CYP = cytochrome P; DLV = delavirdine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NVP = nevirapine; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TB = tuberculosis; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TPV/r = tipranavir/ritonavir

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Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 15)

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

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

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV, ATV/c, ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; ↔ in APV C_{min}	Give FPV simultaneously with (or at least 2 hours before or 1 hour after) antacids.
	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 ART-naive 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 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	No significant effect shown or expected	No dosage adjustment necessary.
	FPV (unboosted)	APV AUC ↓ 30%; no significant change in APV C_{min}	If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
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	No significant effect expected	No dosage adjustment necessary.
	DRV/r	omeprazole AUC ↓ 42%	No dosage adjustment necessary.
	FPV, FPV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
	TPV/r	↓ omeprazole	May need to increase omeprazole dose.
Anticoagulants and Antiplatelets			
Apixaban	All PIs	↑ apixaban expected	**Avoid concomitant use.**
Dabigatran	All RTV-boosted PIs, ATV/c, DRV/c	↑ dabigatran possible	No dosage adjustment if CrCl >50 mL/min. **Avoid coadministration if CrCl <50 mL/min.**
Edoxaban	All PIs	↑ edoxaban	Avoid concomitant use.
Rivaroxaban	All PIs	↑ rivaroxaban	**Avoid concomitant use.**
Ticagrelor	All PIs	↑ ticagrelor expected	**Avoid concomitant use.**
Vorapaxar	All PIs	↑ vorapaxar expected	**Avoid concomitant use.**
Warfarin	PI/r	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.
	ATV/c, DRV/c	No data	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.
Anticonvulsants			
Carbamazepine	ATV, FPV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or ATV/r, ATV/c, or FPV/r.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	ATV/r, FPV/r, LPV/r, SQV/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 or FPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Ethosuximide	All PIs	↑ ethosuximide possible	Clinically monitor for ethosuxamide 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	
	PI/r (other than ATV/r or LPV/r)	↓ lamotrigine possible	
	ATV/c, DRV/c	No data	Monitor lamotrigine concentration or consider alternative anticonvulsant.
Phenobarbital	ATV/c DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	All unboosted PI or 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 or FPV/r once daily, or unboosted ATV or FPV.**
Phenytoin	ATV, FPV (unboosted)	May ↓ PI levels substantially	**Do not coadminister.** Consider alternative anticonvulsant or either ATV/r or FPV/r.
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	ATV/c, DRV/c	↓ cobicistat expected ↓ PI levels expected	**Contraindicated. Do not coadminister.**
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	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.**
Valproic Acid	LPV/r	↓ or ↔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 15)

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.)			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Buspirone	All PIs	↑ buspirone expected	Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (eg, citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	RTV	escitalopram ↔	Titrate SSRI dose based on clinical response.
	DRV/r	paroxetine AUC ↓ 39% sertraline AUC ↓ 49%	
	FPV/r	paroxetine AUC ↓ 55%	
	ATV/r, LPV/r, SQV/r, TPV/r	No data	
	ATV/c, DRV/c	Effects unknown	Titrate SSRI dose using the lowest available initial or maintenance dose.
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.
Other Antipsychotics (eg, perphenazine, risperidone, thioridazine)	ATV/c DRV/c, All PI/r	↑ antipsychotic possible	Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.
Trazodone	All PIs except SQV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not coadminister.**
Tricyclic Antidepressants Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	All PI/r, ATV/c, DRV/c	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	ATV/c, ATV/r	No significant effect observed or expected	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting	No dosage 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%	If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response.
	All PIs except LPV/r	↑ isavuconazole possible ↑ or ↓ PI possible	If coadministered, consider monitoring isavuconazole concentrations. Monitor for PI toxicity and virologic response.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage 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/c	↑ ATV possible	Monitor for adverse effects of ATV.
	ATV/r	ATV AUC ↑ 146%	
	ATV	ATV AUC ↑ 268%	
	FPV	With FPV 700 mg BID (without RTV): posaconazole AUC ↓ 23%, APV AUC similar to that with FPV 1400 mg BID With FPV 1400 mg BID: ↑ APV expected	If coadministered, monitor posaconazole concentrations.
	DRV/c, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ PI possible ↑ posaconazole possible	If coadministered, consider monitoring posaconazole concentrations. Monitor for PI adverse effects.
Voriconazole	ATV, FPV (unboosted)	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	All PI/r	RTV 400 mg BID ↓ voriconazole AUC 82% 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
	ATV/c, DRV/c	Effects unknown	
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%	

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 15)

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	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage 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 non-tuberculosis mycobacterial infections)			
Bedaquiline	All PI/r, ATV/c, DRV/c	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 (eg, azithromycin).
	All PI/r, ATV/c, DRV/c	↑ clarithromycin expected	Consider alternative macrolide (eg, azithromycin)
		DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (eg, 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.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.
Rifabutin	ATV (unboosted)	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
	FPV (unboosted)	No data	Consider alternative ARV.
	ATV/c, DRV/c	↑ rifabutin 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 HIV-infected patients than in the healthy study participants.
	ATV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg once daily) with ATV/r, rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101%	
	DRV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with DRV/r, rifabutin AUC ↔ and metabolite AUC ↑ 881%	

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections), continued			
Rifabutin, continued	FPV/r	Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with FPV/r, rifabutin and metabolite AUC ↑ 64%.	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 HIV-infected patients than in the healthy study participants.
	LPV/r	Compared with rifabutin (300 mg daily) alone, rifabutin (150 mg once daily) with LPV/r, rifabutin and metabolite AUC ↑ 473%.	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin and metabolite AUC ↑ 333%	
Rifampin	All PIs	↓ PI concentration by >75%	**Do not coadminister rifampin and PIs.** 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 dosage adjustment necessary.
Cardiac Medications			
Amiodarone	SQV/r, TPV/r	↑ both amiodarone and PI possible	**Do not coadminister.**
	All PIs (except SQV/r, TPV/r)	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
Antiarrhythmics (eg, dofetilide, dronedarone, flecainide, lidocaine, propafenone, quinidine)	SQV/r	↑ antiarrhythmic possible	**Do not coadminister.**
	All PIs	↑ antiarrhythmic possible	Use with caution. **Refer to Table 18 for contraindicated combinations.**
Beta-blockers (eg, 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 (eg, 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 10 days after PI initiation restart bosentan at 62.5 mg once daily or every other day. When switching between COBI and RTV: • Maintain same bosentan dose.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 8 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
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 used with ATV and SQV.
Digoxin	PI/r, ATV/c, or DRV/c	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43% SQV/r ↑ digoxin AUC 49% DRV/r ↑ digoxin AUC 36% COBI ↑ digoxin C_{max} 41%, 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 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, FPV/r, FPV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Eplerenone	All PIs	↑ eplerenone expected	**Contraindicated. Do not coadminister.**
Ivabradine	All PIs	↑ ivabradine expected	**Contraindicated. Do not coadminister.**
Cortocosteroids			
Beclomethasone Inhaled	DRV/r	RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ C_{max} 1.6-fold (DRV 600 mg + RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ C_{max} 19%	No dosage adjustment necessary. Significant interaction between beclomethasone (inhaled or intranasal) and other PI/r, ATV/c, or DRV/c is not expected.
Budesonide Systemic	All PIs	↓ PI levels possible ↑ glucocorticoids	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.**
Budesonide, Fluticasone, Mometasone Inhaled or Intranasal	All PI/r, ATV/c, DRV/c	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-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 systemic corticosteroid adverse effects.** Consider alternative corticosteroid (eg, beclomethasone).
Dexamethasone Systemic	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use.
Prednisone	LPV/r	↑ prednisolone AUC 31%	Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.**
	All PIs	↑ prednisolone possible	
Methyl-prednisolone, Prednisolone, Triamcinolone (local injections, including intra-articular, epidural, intra-orbital)	All PI/r, ATV/c, DRV/c	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 9 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	ATV/c or ATV/r SQV/r	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
	DRV/c DRV/r LPV/r ATV (unboosted) FPV/r or FPV (unboosted)	↔ daclatasvir	No dose adjustment necessary.
	TPV/r	No data	No dosing recommendations at this time.
Dasabuvir + Paritaprevir/ Ombitasvir/RTV	ATV	ATV ↔	ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir + 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, FPV, SQV, TPV	No data	**Do not coadminister.**
Elbasvir/ grazoprevir	ATV/r	elbasvir AUC ↑ 4.8 fold grazoprevir AUC ↑ 10.6 fold ATV ↔ by elbasvir ATV AUC ↑ 43% by grazoprevir	**Contraindicated. Do not coadminister.** 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, ATV/c, DRV/c, SQV/r, TPV/r	↑ grazoprevir expected	
	FPV/r FPV (unboosted)	No data	No dosing recommendations at this time.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 10 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Ledipasvir/ Sofosbuvir	ATV/r	ATV AUC ↑ 33% ledipasvir AUC ↑ 113% sofosbuvir: no significant effect	No dosage 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: no significant effect expected ledipasvir/sofosbuvir: no significant effect	
	ATV/c, DRV/c, FPV, FPV/r, LPV/r, SQV/r	No significant effect expected	
	TPV/r	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**
Simeprevir	All PIs	Compared with simeprevir 150 mg alone, simeprevir 50 mg plus DRV/r 800/100 mg daily, simeprevir AUC ↑ 159% RTV 100 mg BID ↑ simeprevir AUC 618%	**Do not coadminister.**
Sofosbuvir	TPV/r	↓ sofosbuvir expected	**Do not coadminister.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
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 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.[c]
	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.[b] Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	ATV/c, DRV/c	Effects unknown	Consider alternative or additional contraceptive method or alternative ARV drug.
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ethinyl estradiol AUC ↓ 37% to 48% norethindrone AUC ↓ 14% to 34% With TPV/r: norethindrone AUC ↔	Consider alternative or additional contraceptive method or alternative ARV drug.
	FPV	With APV: ↑ ethinyl estradiol ↑ norethindrone C_{min} APV C_{min} ↓ 20%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.[c] Oral contraceptives containing progestins other than norethindrone have not been studied.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives, continued			
Depot medroxy-progesterone acetate (MPA) injectable	LPV/r	MPA AUC ↑46%; C_{min} no significant change	Use standard dose.
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.
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.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV, ATV/c, ATV/r, DRV/c	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r FPV, FPV/r, SQV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone FPV +/– RTV ↑ atorvastatin AUC 130% to 153% SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31%, C_{max} ↑ 60% ATV: no significant effect DRV/r: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
Pravastatin	ATV/c, ATV/r	No data	Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects.
	DRV/c, DRV/r	With DRV/r, pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 12 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors, continued			
Rosuvastatin	ATV/c, DRV/c	↑ rosuvastatin possible	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C_{max} ↑7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	FPV +/- RTV	No significant effect on rosuvastatin	No dosage adjustment necessary.
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dosage adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin level: SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	Contraindicated. Do not coadminister.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	All PIs	↑ immunosuppressant expected	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immuno-suppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Narcotics and Treatment for Opioid Dependence			
Buprenorphine sublingual/ buccal/implant	ATV (unboosted)	buprenorphine AUC ↑ 93% norbuprenorphine[d] AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.**
	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.
	ATV/c, DRV/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.
	DRV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↑ 46% and C_{min} ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	FPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC ↓ 15%	
	LPV/r	No significant effect	
	TPV/r	buprenorphine: no significant effect norbuprenorphine[d] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19% to 40%	Consider monitoring TPV level. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 13 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics and Treatment for Opioid Dependence, continued			
Fentanyl	All PIs	↑ fentanyl possible	Clinical monitoring is recommended, including for potentially fatal respiratory depression.
Methadone	ATV (unboosted)	No significant effect	No dosage adjustment necessary.
	ATV/c, DRV/c	Effects unknown	Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended.
	FPV (unboosted)	No data with unboosted FPV APV ↓ R-methadone[e] C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar to that with APV.
	All PI/r	ATV/r, DRV/r, and FPV/r ↓ R-methadone[e] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53% SQV/r 1000/100 mg BID ↓ R-methadone[e] AUC 19% TPV/r ↓ R-methadone[e] AUC 48%	Opioid withdrawal 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	LPV/r	oxycodone AUC ↑ 2.6-fold	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary.
Tramadol	ATV/c, DRV/c	↑ tramadol possible	Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Avanafil	All PIs except unboosted ATV and FPV	RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, C_{max} 2.4-fold	**Coadministration is not recommended.**
	ATV, FPV (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% SQV unboosted ↑ sildenafil AUC 210%	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. Do not coadminister.**

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 14 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phosphodiesterase Type 5 (PDE5) Inhibitors, continued			
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124% TPV/r (1st dose) ↑ tadalafil AUC 133% TPV/r steady state: no significant effect	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 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 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 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 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 SQV/r ↑ midazolam (oral) AUC 1144% and C_{max} 327%	**Do not coadminister oral midazolam and 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.**
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	**Do not coadminister.**
Zolpidem	PI/r or ATV/c or DRV/c	↑ zolpidem possible	Initiate zolpidem at a low dose. Dose reduction may be necessary.

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Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 15 of 15)

Concomitant Drug	PI	Effect on PI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs with or without COBI or RTV: significant ↑ colchicine expected	For Treatment of Gout Flares: • Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV:* • 1.2 mg x 1 dose and no repeat dose for at least 3 days For Prophylaxis of Gout Flares: • Colchicine 0.3 mg once daily or every other day *With FPV without RTV:* • Colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For Treatment of Familial Mediterranean Fever: • Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV:* • Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
Flibanserin	All PIs	↑ flibanserin expected	**Contraindicated. Do not coadminister.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events.

[a] DHA is an active metabolite of artemether.

[b] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation 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.

[c] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation 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.

[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; APV = amprenavir; 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; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; HCV = hepatitis C virus; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MPA = medroxyprogesterone acetate; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitorritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid

Note: FPV is a prodrug of APV.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 7)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a and 20b.

Note: DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

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%, C_{min} ↓ 33%	**Contraindicated. Do not coadminister.**
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	Carbamazepine plus EFV: • Carbamazepine AUC ↓ 27% • EFV AUC ↓ 36% Phenytoin plus EFV: • ↓ EFV • ↓ phenytoin possible	Monitor anticonvulsant and EFV levels 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 levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Oxcarbazepine	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	Bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	EFV, ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	Sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage 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.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Isavuconazole	EFV, ETR, NVP	↓ isavuconazole possible	Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole level and antifungal response.
	RPV	↓ isavuconazole possible (likely to a lesser extent than with other NNRTIs) ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
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 possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↓ itraconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Posaconazole	EFV	Posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↓ posaconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.
Voriconazole	EFV	Voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Dose adjustment: • Voriconazole 400 mg BID, EFV 300 mg daily
	ETR	Voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↓ voriconazole possible ↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 7)

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 and malaria recurrence.
	ETR	Artemether AUC ↓ 38% DHA AUC ↓ 15% Lumefantrine AUC ↓ 13% ETR AUC ↑ 10%	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor closely for antimalarial efficacy.
	NVP	Artemether AUC ↓ 67% to 72% DHA: • Study results are conflicting. 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 dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials			
Bedaquiline	EFV	↓ bedaquiline possible	Not recommended.
	NVP	↔ bedaquiline AUC	No dosage 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%	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	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 ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: • Rifabutin 300 mg once daily **if** ETR is not coadministered with a PI/r.
	NVP	Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone: ↔ RPV AUC, C_{min}	Increase RPV dose to 50 mg once daily.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20% to 58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not coadminister.**
Rifapentine	EFV	↔ EFV concentrations	No dosage adjustment necessary.
	ETR, NVP, RPV	↓ NNRTI possible	**Do not coadminister.**
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.
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	Lorazepam C_{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine CCBs	EFV, 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.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP 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 C_{min} ↓ 17%, following daclatasvir 120 mg once daily + EFV 600 mg daily	Daclatasvir 90 mg once daily.
	RPV	No data	No dosage adjustment necessary.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 7)

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			
Dasabuvir plus Paritaprevir/ Ombitasivir/RTV	EFV	No data	**Contraindicated. Do not coadminister.**
	ETR, NVP	↓ DAAs possible	**Do not coadminister.**
	RPV	RPV AUC ↑ 150% to 225%	**Do not coadminister because of potential for QT interval prolongation with higher concentrations of RPV.**
Elbasvir/Grazoprevir	EFV	Elbasvir AUC ↓ 54% Grazoprevir AUC ↓83% EFV ↔ by grazoprevir EFV ↔ AUC by elbasvir	**Contraindicated**.
	ETR, NVP	↓ elbasvir, grazoprevir expected	**Do not coadminister.**
	RPV	Elbasvir, grazoprevir and RPV ↔	No dosage adjustment necessary.
Ledipasvir/ Sofosbuvir	EFV	Ledipasvir AUC, C_{min}, C_{max} – all ↓ 34% Sofosbuvir: no significant effect	No dosage adjustment necessary.
	ETR, NVP, RPV	No significant effect expected	
Simeprevir	EFV	Simeprevir AUC ↓ 71%, C_{min} ↓ 91% ↔ EFV	**Coadministration is not recommended.**
	ETR, NVP	↓ simeprevir expected	**Coadministration is not recommended.**
	RPV	↔ simeprevir and RPV	No dosage adjustment necessary.
Herbal Products			
St. John's Wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives	EFV	Ethinyl estradiol ↔ Levonorgestrel (oral) AUC ↓ 64% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓ 63% Levonorgestrel (implant) AUC ↓ 48%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate. Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly.
	ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	Ethinyl estradiol AUC ↓ 29%, C_{min} ↓ 58% Norethindrone AUC ↓ 18% Etonogestrel (metabolite of oral desogestrel) ↓ 22%	Consider alternative or additional contraceptive methods.
		DMPA: no significant change	No dosage adjustment necessary.
		Levonorgestrel implant: AUC ↑ 30%	No dosage adjustment necessary.
	RPV	Ethinyl estradiol: no significant change Norethindrone: no significant change	No dosage adjustment necessary.

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Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	EFV	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to 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, not to 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 ↓ 11%, C_{max} ↑ 20%	No dosage adjustment necessary.
	ETR, NVP, RPV	No data	No significant effect expected. No dosage adjustment necessary.
Pravastatin **Rosuvastatin**	EFV	Pravastatin AUC ↓ 44% Rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.
Immunosuppressants			
Cyclosporine **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/buccal	EFV	Buprenorphine AUC ↓ 50% Norbuprenorphine[b] AUC ↓ 71%	No dosage adjustment recommended; monitor for withdrawal symptoms.
	ETR	Buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	NVP	No significant effect	No dosage 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.
	ETR	No significant effect	No dosage adjustment necessary.
	NVP	Methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.

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Table 19b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 7)

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	EFV, ETR, NVP, RPV	No data	**Coadministration is not recommended.**
Sildenafil	ETR	Sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	↔ sildenafil	No dosage adjustment necessary.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 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 blockers; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; 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 jiroveci* pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir

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Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Non-ARV Antivirals			
Adefovir	TDF	No data	**Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased.
Ganciclovir **Valganciclovir**	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant effect	Potential increase in hematologic toxicities
Ledipasvir/ Sofosbuvir	TAF	No significant effect	No dose adjustment
	TDF	• Ledipasvir ↑ TDF AUC 40% to 98% when TDF given with RPV and EFV • Further ↑ TDF possible if TDF given with PIs	No dose adjustment necessary. Monitor for TDF toxicity. The safety of increased TDF exposure when ledipasvir/sofosbuvir is coadministered with TDF and a PI/r, ATV/c, or DRV/c 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. Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC **is not recommended**.
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	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 dosage adjustment
	TDF	• TDF AUC ↑ 12% and C_{min} ↑ 19% • DTG ↔	No dosage adjustment
RAL	TDF	RAL AUC ↑ 49%	No dosage adjustment
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, TAF, ZDV	No significant effect	No dosage adjustment
Methadone	ABC	Methadone clearance ↑ 22%	No dosage adjustment
	d4T	d4T AUC ↓ 23%	No dosage adjustment
	ZDV	ZDV AUC ↑ 29% to 43%	Monitor for ZDV-related adverse effects.
NNRTIs			
RPV	ddI	RPV, ddI ↔ when RPV taken 2 hours after ddI	Administer RPV with food 4 hours before or 2 hours after ddI.

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Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
NRTIs			
ddI	d4T	No significant PK interaction	**Do not coadminister.** Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48% to 60%	**Avoid coadministration.**
Other			
Allopurinol	ddI	ddI AUC ↑ 113% In patients with renal impairment: • ddI AUC ↑ 312%	**Contraindicated.** Potential for increased ddI-associated toxicities.
Atovaquone	ZDV	ZDV AUC ↑ 31%	Monitor for ZDV-related adverse effects.
Anticonvulsants Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin	TAF	↓ TAF possible	Consider alternative anticonvulsant.
Antimycobacterial Rifabutin, Rifampin, Rifapentine	TAF	↓ TAF possible	Coadministration is not recommended.
Herbal Products St. John's wort	TAF	↓ TAF possible	Coadministration is not recommended.
PIs			
ATV +/- RTV or COBI	ddI	With ddI-EC plus ATV (with food): • ddI AUC ↓ 34% • ATV no change	Administer ATV with food 2 hours before or 1 hour after ddI.
	TAF	TAF 10 mg with ATV/r: TAF AUC ↑ 91%	No dosage adjustment (use TAF 25mg).
	TDF	With ATV (unboosted): • ATV AUC ↓ 25% and C_{min} ↓ 23% to 40% (higher C_{min} with RTV than without RTV) • TDF 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 ART-experienced patients, 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 AUC ↔	Clinical significance unknown.

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Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 3)

Concomitant Drug Class/Name	NRTI	Effect on NRTI and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
DRV/c	TAF	TAF 25 mg with DRV/c: TAF AUC ↔	No dosage adjustment
	TDF	Increased TDF possible	Monitor for TDF-associated toxicity.
DRV/r	TAF	TAF 10 mg with DRV/r: TAF AUC ↔	No dosage adjustment
	TDF	TDF AUC ↑ 22% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TAF	TAF 10 mg with DRV/r: • TAF AUC ↑ 47%	No dosage adjustment
	TDF	• LPV/r AUC ↓ 15% • TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC AUC ↓ 35% to 44%	Appropriate doses for this combination have not been established.
	ddI	ddI-EC AUC ↔ and C_{min} ↓ 34% TPV/r ↔	Separate doses by at least 2 hours.
	TAF	↓ TAF expected	Coadministration **is not recommended**.
	TDF	• TDF AUC ↔ • TPV/r AUC ↓ 9% to 18% and C_{min} ↓ 12% to 21%	No dosage adjustment necessary.
	ZDV	• ZDV AUC ↓ 35% • TPV/r AUC ↓ 31% to 43%	Appropriate doses for this combination have not been established.

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

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = douletegravir; EC = enteric coated; EFV = efavirenz; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 11)

This table provides information on known or predicted pharamacokinetic interactions between INSTIs (DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with either COBI or RTV. In this table, the drug interactions with EVG/c products and those with EVG plus PI/r are presented separately. When EVG is given with a PI/r, clinicians should refer to Table 19a for recommendations on the management of drug interactions of concomitant medications and the specific PI/r used with EVG.

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Aluminium, Magnesium +/- Calcium-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (eg, iron, calcium supplements, multivitamins).	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 plus PI/r	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 more than 2 hours.
	RAL	Al-Mg Hydroxide Antacid: • RAL C_{min} ↓ 54% to 63% $CaCO_3$ Antacid: • RAL C_{min} ↓ 32%	**Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent. No dosing separation necessary when coadministering RAL and $CaCO_3$ antacids.
H2-Receptor Antagonists	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG	No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions.
PPIs	DTG	No significant effect	No dosage adjustment necessary.
	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG	No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions.
	RAL	RAL AUC ↑ 212% and C_{min} ↑ 46%	No dosage adjustment necessary.
Anticoagulants and Antiplatelets			
Apixaban	EVG/c EVG plus PI/r	↑ apixaban expected	**Avoid concomitant use.**
Dabigatran	EVG/c EVG plus PI/r	↑ dabigatran possible	No dosage adjustment for dabigatran if CrCl >50 mL/min. **Avoid coadministration if CrCl <50 mL/min.**
Edoxaban	EVG/c EVG plus PI/r	↑ edoxaban expected	**Avoid concomitant use.**
Rivaroxaban	EVG/c EVG plus PI/r	↑ rivaroxaban expected	**Avoid concomitant use.**

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants and Antiplatelets, continued			
Ticagrelor	EVG/c EVG plus PI/r	↑ ticagrelor expected	**Avoid concomitant use.**
Vorapaxar	EVG/c EVG plus PI/r	↑ vorapaxar expected	**Avoid concomitant use.**
Warfarin	EVG/c EVG plus PI/r	Warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	DTG	↓ DTG possible	Consider alternative anticonvulsant.
	EVG/c	carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated. Do not coadminister.**
	EVG plus PI/r	↓ EVG	Consider alternative anticonvulsant.
Ethosuximide	EVG/c EVG plus PI/r	↑ ethosuximide possible	Clinically monitor for ethosuxamide toxicities.
Oxcarbazepine	DTG EVG/c EVG plus PI/r	↓ INSTI possible	Consider alternative anticonvulsant.
Antidepressants/Anxiolytics/Antipsychotics Also see Sedative/Hypnotics section below.			
Bupropion	EVG/c	↑ or ↓ bupropion possible	Titrate bupropion dose based on clinical response.
	EVG plus PI/r	↓ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	EVG/c EVG plus PI/r	↑ buspirone possible	Initiate buspirone at a low dose. Dose reduction may be necessary.
Fluvoxamine	EVG/c EVG plus PI/r	↑ or ↓ EVG possible	Consider alternative antidepressant or ARV.
Quetiapine	EVG/c EVG plus PI/r	↑ 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.

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 11)

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.			
SSRIs Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	EVG/c	↑ SSRI possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	EVG plus PI/r	↑ or ↓ SSRI possible	Titrate SSRI dose based on clinical response.
	RAL	↔ RAL ↔ citalopram	No dosage adjustment necessary.
TCAs Amitriptyline Desipramine Doxepin Imipramine Nortriptyline	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
	EVG plus PI/r	↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels.
Trazodone	EVG/c EVG plus PI/r	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Antifungals			
Isavuconazole	EVG/c	↑ isavuconazole expected ↑ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assess virologic response.
	EVG plus PI/r	Changes in isavuconazole and EVG possible	Refer to Table 19a for PI recommendations.
Itraconazole	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.
	EVG plus PI/r	↑ EVG possible	Refer to Table 19a for PI recommendations.
Posaconazole	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
	EVG plus PI/r	↑ EVG possible	Refer to Table 19a for PI recommendations.
Voriconazole	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly.
	EVG plus PI/r	Changes in voriconazole and EVG possible	Refer to Table 19a for PI recommendations.

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 11)

Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials			
Clarithromycin	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.
Rifabutin	DTG	Rifabutin (300 mg once daily): • DTG AUC ↔ and C_{min} ↓ 30%	No dosage 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%, C_{min} ↓ 67%	**Do not coadminister.**
	EVG plus PI/r	↔ EVG ↔ rifabutin AUC 25-O-desacetyl-rifabutin AUC ↑ 951%	Refer to Table 19a for dosing recommendations for rifabutin with PI.
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dosage adjustment necessary.
Rifampin	DTG	Rifampin with DTG 50 mg BID compared to DTG 50 mg BID alone: DTG AUC ↓ 54%, C_{min} ↓ 72% Rifampin with DTG 50 mg BID compared to DTG 50 mg once daily alone: DTG AUC ↑ 33%, 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 EVG plus PI/r	Significant ↓ EVG and COBI expected	**Do not coadminister.**
	RAL	RAL 400 mg: • RAL AUC ↓ 40%, C_{min} ↓ 61% Compared with RAL 400 mg BID alone, Rifampin with RAL 800 mg BID: • RAL AUC ↑ 27%, C_{min} ↓ 53%	Dose: • RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin.
Rifapentine	DTG	Significant ↓ DTG expected	**Do not coadminister.**
	EVG/c EVG plus PI/r	Significant ↓ EVG and COBI expected	**Do not coadminister.**
	RAL	Rifapentine 600 mg once daily: RAL C_{min} ↓ 41% Rifapentine 900 mg once weekly: RAL AUC ↑ 71%, C_{min} ↓ 12%	**Do not coadminister with once-daily rifapentine.** For once-weekly rifapentine, use standard doses.

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 11)

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	EVG/c	↑ antiarrhythmics possible digoxin C_{max} ↑ 41% and AUC no significant change	Use antiarrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for antiarrhythmics.
	EVG plus PI/r	↑ antiarrhythmics possible	Refer to Table 18 and 19a for use of antiarrhythmics and PI/r.
Bosentan	EVG/c	↑ bosentan possible	In patients on EVG/c ≥10 days: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In patients on bosentan who require EVG/c: • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
	EVG plus PI/r	↑ bosentan possible	Refer to Table 19a for recommendations on bosentan dosing when used with PI/r.
Beta-blockers (eg, metoprolol, timolol)	EVG/c EVG plus PI/r	↑ 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 (eg, atenolol, labetalol, nadolol, sotalol).
CCBs	EVG/c EVG plus PI/r	↑ CCBs possible	Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities. Refer to Table 19a for diltiazem plus ATV/r and SQV/r recommendations.
Dofetilide	DTG	↑ dofetilide expected	**Do not coadminister.**
Eplerenone	EVG/c EVG plus PI/r	↑ eplerenone expected	**Contraindicated. Do not coadminister.**
Ivabradine	EVG/c EVG plus PI/r	↑ ivabradine expected	**Contraindicated. Do not coadminister.**

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Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids			
Dexamethasone (systemic)	EVG/c	↓ EVG and COBI possible	Use systemic dexamethasone with caution. Monitor virologic response to ART. Consider alternative corticosteroid.
	EVG plus PI/r	↓ EVG possible	
Fluticasone Inhaled/Intranasal	EVG/c EVG plus PI/r	↑ fluticasone possible	Coadministration may result in adrenal insufficiency and Cushing's syndrome. Consider alternative therapy (eg, beclo-methasone), particularly for long-term use.
Methylprednisolone **Prednisolone** **Triamcinolone** Local injections, including intra-articular, epidural, intra-orbital	EVG/c EVG plus PI/r	↑ glucocorticoids expected	Coadministration may result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister.**
Hepatitis C Direct Acting Antivirals			
Daclatasvir	DTG	↔ Daclatasvir	No dosage adjustment necessary.
	EVG/c	↑ Daclatasvir	Decrease daclastavir dose to 30 mg once daily.
	EVG plus PI/r	↑ Daclatasvir expected	Decrease daclastavir dose to 30 mg once daily, regardless of which PI/r is used, except for TPV/r. Do not coadminister EVG plus TPV/r with daclastavir.
	RAL	No data	No dosage adjustment necessary.
Dasabuvir plus Ombitasvir/Paritaprevir/r	DTG	No data	No dosing recommendations at this time.
	EVG plus PI/r EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dosage adjustment necessary.
Elbasvir/Grazoprevir	DTG	↔ Elbasvir ↔ Grazoprevir ↔ DTG	No dosage adjustment necessary.
	EVG plus PI/r		Refer to Table 19a for PI dosing recommendations.
	EVG/c	↑ elbasvir, grazoprevir expected	**Coadministration is not recommended.**
	RAL	↔ Elbasvir ↔ Grazoprevir RAL ↔ with elbasvir RAL AUC ↑ 43% with grazoprevir	No dosage adjustment necessary.
Ledipasvir/Sofosbuvir	EVG/c	↑ TDF and ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c	↔ EVG/c/TAF/FTC expected	No dosage adjustment necessary.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for PI dosing recommendations.
	DTG RAL	↔ DTG or RAL	No dosage adjustment necessary.

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Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct Acting Antivirals, continued			
Simeprevir	DTG	↔ DTG expected	No dosage adjustment necessary.
	EVG/c	↑ simeprevir expected	**Coadministration is not recommended.**
	EVG plus PI/r	↔ EVG expected	**Coadministration is not recommended.**
	RAL	No significant effect	No dosage adjustment necessary.
Sofosbuvir	All INSTIs	No significant effect expected	No dosage adjustment necessary.
Herbal Products			
St. John's Wort	DTG	↓ DTG possible	**Do not coadminister.**
	EVG/c EVG plus PI/r	↓ EVG and COBI possible	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives	RAL	No clinically significant effect	No dosage adjustment necessary.
Norgestimate/Ethinyl Estradiol	DTG	No significant effect	No dosage 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 alternative contraceptive method.
	EVG plus PI/r	↔ EVG	Refer to Table 19a for recommendations when used with PI/r.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EVG/c	↑ atorvastatin possible	Titrate statin dose slowly and use the lowest dose possible.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Lovastatin	EVG/c EVG plus PI/r	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin **Pravastatin**	EVG/c	No data	No dosage recommendation
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Rosuvastatin	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose slowly and use the lowest dose possible.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
Simvastatin	EVG/c EVG plus PI/r	Significant ↑ simvastatin expected	**Contraindicated. Do not coadminister.**

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Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Immunosuppressants			
Cyclosporine **Everolimus** **Sirolimus** **Tacrolimus**	EVG/c EVG plus PI/r	↑ 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 specialist as necessary.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine Sublingual/Buccal/Implant	EVG/c	Buprenorphine AUC ↑ 35%, C_{max} ↑ 12%, and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42%, C_{max} ↑ 24%, and C_{min} ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	EVG plus PI/r	↔ EVG expected	Refer to Table 19a for dosing recommendations when used with PI/r.
	RAL	No significant effect observed (sublingual) or expected (implant)	No dosage adjustment necessary.
Methadone	DTG	No significant effect	No dosage adjustment necessary.
	EVG/c	No significant effect	No dosage adjustment necessary.
	EVG plus PI/r	↓ methadone	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	RAL	No significant effect	No dosage adjustment necessary.
Neuroleptics			
Perphenazine **Risperidone** **Thioridazine**	EVG/c	↑ neuroleptic possible	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary.
PDE5 Inhibitors			
Avanafil	EVG/c EVG plus PI/r	No data	**Coadministration is not recommended.**
Sildenafil	EVG/c EVG plus PI/r	↑ 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**

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Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors, continued			
Tadalafil	EVG/c EVG plus PI/r	↑ tadalafil expected	For treatment of erectile dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 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 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 40 mg once daily based on tolerability.
Vardenafil	EVG/c EVG plus PI/r	↑ 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**	EVG/c EVG plus PI/r	↑ 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**	DTG	With DTG 25 mg: midazolam AUC ↔	No dosage adjustment necessary.
	EVG/c EVG plus PI/r	↑ midazolam expected ↑ triazolam expected	**Do not coadminister triazolam or oral midazolam and EVG/c or (EVG plus PI).** Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered.
Suvorexant	EVG/c EVG plus PI/r	↑ suvorexant expected	**Coadministration is not recommended.**
Zolpidem	EVG/c EVG plus PI/r	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary.

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Concomitant Drug Class/Name	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs			
Colchicine	EVG/c EVG plus PI/r	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** For treatment of gout flares: • Colchicine 0.6 mg for 1 dose, followed by 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.
Flibanserin	EVG/c EVG plus PI/r	↑ flibanserin expected	**Contraindicated. Do not coadminister.**
Metformin	DTG	DTG 50 mg once daily plus metformin 500 mg BID: Metformin AUC ↑ 79%, C_{max} ↑ 66% DTG 50 mg BID plus metformin 500 mg BID: Metformin AUC ↑ 2.4 fold, C_{max} ↑ 2 fold	Limit metformin dose to no more than 1,000 mg per day. When starting/stopping DTG in patient on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize GI symptoms.
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.	All INSTIs	↓ INSTI possible DTG ↔ when administered with Ca or Fe supplement simultaneously with food	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. DTG and supplements containing Ca or Fe can be taken simultaneously with food. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.
Salmeterol	EVG/c EVG plus PI/r	↑ salmeterol possible	**Do not coadminister** due to potential increased risk of salmeterol-associated cardiovascular events.

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Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 11)

Key to Acronyms: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; Ca = calcium; CaCO3 = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; c or COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; GI = gastrointestinal; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; SQV/r = saquanavir/ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; Zn = zinc

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Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)

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, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	**Coadministration is not recommended.** If coadministration is necessary, use MVC 600 mg BID. If coadministered 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 for daclatasvir. MVC dose 300 mg BID.**
Dasabuvir + Ombitasvir/ Paritaprevir/RTV	MVC	↑ MVC expected	**Do not coadminister.**
Elbasvir/ Grazoprevir	MVC	No data	No dosing recommendations at this time
Ledipasvir/ Sofosbuvir	MVC	↔ MVC expected ↔ Daclatasvir expected	Dose: • MVC 300 mg BID
Simeprevir	MVC	↔ MVC expected	Dose: • MVC 300 mg BID
Sofosbuvir	MVC	↔ MVC expected	Dose: • MVC 300 mg BID

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Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Herbal Products			
St. John's Wort	MVC	↓ MVC possible	**Coadministration is not recommended.**
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
ARV Drugs			
INSTIs			
EVG/c	MVC	↑ MVC possible	**Do not coadminister.**
EVG + PI/r	MVC	No data	Refer to PIs listed below for dosing recommendations when MVC is used with a PI/r.
RAL	MVC	MVC AUC ↓ 21% RAL AUC ↓ 37%	Dose: • Standard
NNRTIs			
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 +/- RTV or COBI	MVC	With Unboosted ATV: • MVC AUC ↑ 257% With (ATV 300 mg Plus RTV 100 mg) Once Daily: • MVC AUC ↑ 388%	Dose: • MVC 150 mg BID
DRV/r or DRV/c	MVC	With (DRV 600 mg Plus RTV 100 mg) BID: • MVC AUC ↑ 305% With (DRV 600 mg Plus RTV 100 mg) BID and ETR: • MVC AUC ↑ 210%	Dose: • MVC 150 mg BID
FPV +/- RTV	MVC	With (FPV 700 mg Plus RTV 100 mg) BID and MVC 300 mg BID: • MVC AUC ↑ 149%, C_{min} ↑ 374% With (FPV 1400 mg Plus RTV 200 mg) Once Daily and MVC 300 mg Once Daily: • MVC AUC ↑ 126%, C_{min} ↑ 80%	Dose: • MVC 150 mg BID
LPV/r	MVC	MVC AUC ↑ 295% With LPV/r and EFV: • MVC AUC ↑ 153%	Dose: • MVC 150 mg BID

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Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (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			
RTV	MVC	With RTV 100 mg BID: • MVC AUC ↑ 161%	Dose: • MVC 150 mg BID
SQV/r	MVC	With (SQV 1000 mg Plus RTV 100 mg) BID: • MVC AUC ↑ 877% With (SQV 1000 mg Plus RTV 100 mg) BID and EFV: • MVC AUC ↑ 400%	Dose: • MVC 150 mg BID
TPV/r	MVC	With (TPV 500 mg Plus RTV 200 mg) BID: • MVC AUC ↔	Dose: • MVC 300 mg BID

Note: FPV is a prodrug of APV.

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

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

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Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 1 of 3)

Note: DLV, IDV, and NFV are **not** included in this table. Refer to the DLV, IDV, and NFV Food and Drug Administration package inserts for information regarding drug interactions.

PIs		NNRTIs			
		EFV	**ETR**	**NVP**	**RPV[a]**
ATV Unboosted	**PK Data**	EFV: no significant change ATV AUC ↓ 74%	ETR AUC ↑ 50% and C_{min} ↑ 58% ATV AUC ↓ 17% and C_{min} ↓ 47%	↓ ATV possible	↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/c	**PK Data**	↓ ATV ↓ COBI	↓ ATV ↓ COBI	↓ COBI	↑ RPV possible ↔ ATV expected
	Dose	EFV standard dose In ART-Naive Patients: • ATV 400 mg plus COBI 150 mg Once Daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV/r	**PK Data**	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV concentrations are similar to those with unboosted ATV without EFV.	(ATV 300 mg plus RTV 100 mg) Once Daily: • ETR AUC and C_{min} both ↑ ~30% • ATV AUC ↔ and C_{min} ↓ 18%	(ATV 300 mg plus RTV 100 mg) Once Daily: • ATV AUC ↓ 42% and C_{min} ↓ 72% • NVP AUC ↑ 25%	↑ RPV possible
	Dose	EFV standard dose In ART-Naive Patients: • (ATV 400 mg plus RTV 100 mg) Once Daily **Do not coadminister in ART-experienced patients.**	ETR standard dose (ATV 300 mg plus RTV 100 mg) Once Daily	**Do not coadminister.**	Standard doses
DRV/c	**PK Data**	↓ DRV possible ↓ COBI possible	Effect on DRV unknown ↓ COBI possible	Effect on DRV unknown ↓ COBI possible	↔ DRV expected ↑ RPV possible
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	Standard doses

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Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 2 of 3)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
DRV/r	PK Data	With (DRV 300 mg plus RTV 100 mg) BID: • EFV AUC ↑ 21% • DRV AUC ↓ 13% 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: no significant change	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: no significant change
	Dose	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard doses Safety and efficacy of this combination, despite reduced ETR concentration, have been established in a clinical trial.	Standard doses	Standard doses
FPV +/- RTV	PK Data	With (FPV 1400 mg plus RTV 200 mg) Once Daily: • APV C_{min} ↓ 36%	With (FPV 700 mg plus RTV 100 mg) BID: • APV AUC ↑ 69% and C_{min} ↑ 77%	With Unboosted FPV 1400 mg BID: • NVP AUC ↑ 29% • APV AUC ↓ 33% With (FPV 700 mg plus RTV 100 mg) BID: • NVP C_{min} ↑ 22%	With Boosted and Unboosted FPV: • ↑ RPV possible
	Dose	(FPV 1400 mg plus RTV 300 mg) Once Daily **or** (FPV 700 mg plus RTV 100 mg) BID EFV standard dose	**Do not coadminister with FPV +/− RTV.**	(FPV 700 mg plus RTV 100 mg) BID NVP standard dose	Standard doses
LPV/r	PK Data	With LPV/r Tablets 500/125 mg[c] BID: • LPV concentration similar to that with LPV/r 400/100 mg BID without EFV	With LPV/r Tablets: • ETR AUC ↓ 35% (comparable to the decrease with DRV/r) • LPV AUC ↓ 13%	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 no significant change
	Dose	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 520/130 mg BID EFV standard dose	Standard doses	LPV/r tablets 500/125 mgc BID; LPV/r oral solution 533/133 mg BID NVP standard dose	Standard doses

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Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 3 of 3)

PIs		NNRTIs			
		EFV	ETR	NVP	RPV[a]
SQV Always use with RTV	**PK Data**	With SQV 1200 mg TID: • EFV AUC ↓ 12% • SQV AUC ↓ 62%	With (SQV 1000 mg plus RTV 100 mg) BID: • ETR AUC ↓ 33% and C_{min} ↓ 29% • SQV AUC ↔ ↓ ETR levels similar to reduction with DRV/r	With SQV 600 mg TID: • NVP: no significant change • SQV AUC ↓ 24%	↑ RPV possible
	Dose	(SQV 1000 mg plus RTV 100 mg) BID	(SQV 1000 mg plus RTV 100 mg) BID	Dose with SQV/r not established	Standard doses
TPV Always use with RTV	**PK Data**	With (TPV 500 mg plus RTV 100 mg) BID: • EFV no significant change • TPV AUC ↓ 31% and C_{min} ↓ 42% With (TPV 750 mg plus RTV 200 mg) BID: • EFV: no significant change • TPV: no significant change	With (TPV 500 mg plus RTV 200 mg) BID: • ETR AUC ↓ 76% and C_{min} ↓ 82% • TPV AUC ↑ 18% and C_{min} ↑ 24%	With (TPV 250 mg plus RTV 200 mg) BID or with (TPV 750 mg plus RTV 100 mg) BID: • NVP: no significant change • TPV: no data	↑ RPV possible
	Dose	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 75 mg to 150 mg RPV per dose.

[b] Based on between-study comparison.

[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: APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TID = three times a day; TPV = tipranavir

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Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
NNRTIs					
EFV	**PK Data**	With DTG 50 mg once daily: • DTG AUC ↓ 57% and C_{min} ↓ 75%	↑ or ↓ EVG, COBI, EFV possible	↓ EVG expected	RAL: • AUC ↓ 36%
	Dose	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.**	**Do not coadminister.**	Standard doses
ETR	**PK Data**	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	No significant interaction between EVG/r and ETR	• ETR C_{min} ↓ 17% • RAL C_{min} ↓ 34%
	Dose	**Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.** In patients without INSTI resistance: • DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r) In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance: • DTG 50 mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r)	**Do not coadminister.**	May coadminister EVG with ETR plus (ATV/r, DRV/r, or LPV/r) EVG: • Standard dose depending on the concomitant PI (see below)	Standard doses

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Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
NNRTIs, continued					
NVP	**PK Data**	With DTG 50 mg once daily: DTG AUC ↓ 19% and C_{min} ↓ 34%	↑ or ↓ EVG, COBI, NVP possible	↓ EVG possible	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses
RPV	**PK 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 expected	• RPV ↔ • RAL C_{min} ↑ 27%
	Dose	Standard doses	**Do not coadminister.**	EVG: • Standard dose depending on the concomitant PI (see below) RPV: • Standard dose	Standard doses
PIs					
ATV/c	**PK Data**	No data	ATV/c plus EVG/c: • No data	No data	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses
ATV +/- RTV	**PK Data**	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	EVG 85 mg with (ATV 300 mg plus RTV 100 mg) once daily: • EVG AUC ↔ and C_{min} ↑ 38% • ATV AUC and C_{min} ↔	With unboosted ATV: • RAL AUC ↑ 72% With (ATV 300 mg plus RTV 100 mg) once daily: • RAL AUC ↑ 41%
	Dose	Standard doses	**Do not coadminister.**	• EVG 85 mg once daily • (ATV 300 mg plus RTV 100 mg) once daily	Standard doses
DRV/c	**PK Data**	No data	DRV/c plus EVG/c: • ↓ EVG possible	No data	No data
	Dose	Standard doses	**Do not coadminister.**	**Do not coadminister.**	Standard doses

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Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
PIs, continued					
DRV/r	**PK 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	EVG 125 mg once daily with (DRV 600 mg plus RTV 100 mg) BID: • EVG AUC and C_{min} ↔ • DRV AUC and C_{min} ↔	With (DRV 600 mg plus RTV 100 mg) BID: • RAL AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Standard doses: • Once or twice daily dosing of DRV/r	**Do not coadminister.**	• EVG 150 mg once daily • (DRV 600 mg plus RTV 100 mg) BID	Standard doses
FPV +/- RTV	**PK Data**	With (FPV 700 mg plus RTV 100 mg) BID and DTG 50 mg once daily: • DTG AUC ↓ 35% and C_{min} ↓ 49%	↑ or ↓ EVG, COBI, FPV possible	No significant interaction with FPV and EVG	FPV: No significant effect
	Dose	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.**	• EVG 150 mg once daily • (FPV 700 mg plus RTV 100 mg) BID	Standard doses
LPV/r	**PK Data**	With (LPV 400 mg plus RTV 100 mg) BID and DTG 30 mg once daily: • DTG: no significant effect	↑ or ↓ EVG, COBI, LPV possible RTV and COBI have similar effects on CYP3A.	EVG 125 mg once daily with (LPV 400 mg plus RTV 100 mg) BID: • EVG AUC ↑ 75% and C_{min} ↑ 138% • LPV AUC and C_{min} ↔	• ↓ RAL • ↔ LPV/r
	Dose	Standard doses: • Once or twice daily dosing of LPV/r	**Do not coadminister.**	• EVG 85 mg once daily • (LPV 400 mg plus RTV 100 mg) BID	Standard doses
SQV/r	**PK Data**	No data	↑ or ↓ EVG, COBI, SQV possible RTV and COBI have similar effects on CYP3A.	No data	No data
	Dose	Standard doses	**Do not coadminister.**	No dosage recommendation	Standard doses

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Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)

ARV Drugs by Drug Class		INSTIs			
		DTG	EVG/c	EVG (when used with PI/r)	RAL
PIs, continued					
TPV/r	**PK Data**	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.	EVG 200 mg once daily with (TPV 500 mg plus RTV 200 mg) BID: • EVG AUC and C_{min} ↔ • TPV AUC and C_{min} ↔	With (TPV 500 mg plus RTV 200 mg) BID: • RAL AUC ↓ 24%
	Dose	In patients without INSTI resistance: • DTG 50 mg BID In patients with certain INSTI-associated resistancea or clinically suspected INSTI resistance: • **Consider alternative combination.**	**Do not coadminister.**	• EVG 150 mg once daily • (TPV 500 mg plus RTV 200 mg) BID	Standard doses

[a] Refer to dolutegravir product labeling for details.

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

Key to Abbreviations: ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; C_{min} = minimum plasma concentration; COBI, c = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; EVG/r = elvitegravir/ritonavir; FPV = fosamprenavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir

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Preventing Secondary Transmission of HIV (Last updated March 27, 2012; last reviewed March 27, 2012)

Despite substantial advances in prevention and treatment of HIV infection in the United States, the rate of new infections has remained stable.[1-2] Although earlier prevention interventions mainly were behavioral, recent data demonstrate the strong impact of antiretroviral therapy (ART) on secondary HIV transmission. The most effective strategy to stem the spread of HIV will probably be a combination of behavioral, biological, and pharmacological interventions.[3]

Prevention Counseling

Counseling and related behavioral interventions for those living with HIV infection can reduce behaviors associated with secondary transmission of HIV. Each patient encounter offers the clinician an opportunity to reinforce HIV prevention messages, but multiple studies show that prevention counseling is frequently neglected in clinical practice.[4-5] Although delivering effective prevention interventions in a busy practice setting may be challenging, clinicians should be aware that patients often look to their providers for messages about HIV prevention. Multiple approaches to prevention counseling are available, including formal guidance from the Centers for Disease Control and Prevention (CDC) for incorporating HIV prevention into medical care settings. Such interventions have been demonstrated to be effective in changing sexual risk behavior[6-8] and can reinforce self-directed behavior change early after diagnosis.[9]

CDC's "Prevention Is Care" campaign (http://www.actagainstaids.org/provider/pic/index.html) helps providers (and members of a multidisciplinary care team) integrate simple methods to prevent transmission by HIV-infected individuals into routine care. These prevention interventions are designed to reduce the risk of secondary HIV transmission through sexual contact. The interventions are designed generally for implementation at the community or group level, but some can be adapted and administered in clinical settings by a multidisciplinary care team.

Need for Screening for High-Risk Behaviors

The primary care visit provides an opportunity to screen patients for ongoing high-risk drug and sexual behaviors for transmitting HIV infection. Routine screening and symptom-directed testing for and treatment of sexually transmitted diseases (STDs), as recommended by CDC,[10] remain essential adjuncts to prevention counseling. Genital ulcers may facilitate HIV transmission and STDs may increase HIV viral load in plasma and genital secretions.[7, 11-13] They also provide objective evidence of unprotected sexual activity, which should prompt prevention counseling.

The contribution of substance and alcohol use to HIV risk behaviors and transmission has been well established in multiple populations;[14-18] therefore, effective counseling for injection and noninjection drug users is essential to prevent HIV transmission. Identifying the substance(s) of use is important because HIV prevalence, transmission risk, risk behaviors, transmission rates, and potential for pharmacologic intervention all vary according to the type of substance used.[19-21] Risk-reduction strategies for injection drug users (IDUs), in addition to condom use, include needle exchange and instructions on cleaning drug paraphernalia. Evidence supporting the efficacy of interventions to reduce injection drug use risk behavior also exists. Interventions include both behavioral strategies[14-15, 22] and opiate substitution treatment with methadone or buprenorphine.[23-24] No successful pharmacologic interventions have been found for cocaine and methamphetamine users; cognitive and behavioral interventions demonstrate the greatest effect on reducing the risk behaviors of these users.[25-27] Given the significant impact of cocaine and methamphetamine on sexual risk behavior, reinforcement of sexual risk-reduction strategies is important.[14-18, 28]

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Antiretroviral Therapy as Prevention

ART can play an important role in preventing HIV transmission. Lower levels of plasma HIV RNA have been associated with decreases in the concentration of virus in genital secretions.[29-32] Observational studies have demonstrated the association between low serum or genital HIV RNA and a decreased rate of HIV transmission among serodiscordant heterosexual couples.[29, 33-34] Ecological studies of communities with relatively high concentrations of men who have sex with men (MSM) and IDUs suggest increased use of ART is associated with decreased community viral load and reduced rates of new HIV diagnoses.[35-37] These data suggest that the risk of HIV transmission is low when an individual's viral load is below 400 copies/mL,[35, 38] but the threshold below which transmission of the virus becomes impossible is unknown. Furthermore, to be effective at preventing transmission it is assumed that: (1) ART is capable of durably and continuously suppressing viremia; (2) adherence to an effective ARV regimen is high; and (3) there is an absence of a concomitant STD. Importantly, detection of HIV RNA in genital secretions has been documented in individuals with controlled plasma HIV RNA and data describing a differential in concentration of most ARV drugs in the blood and genital compartments exist.[30, 39] At least one case of HIV transmission from a patient with suppressed plasma viral load to a monogamous uninfected sexual partner has been reported.[40]

In the HPTN 052 trial in HIV-discordant couples, the HIV-infected partners who were ART naive and had CD4 counts between 350 and 550 cells/mm^3 were randomized to initiate or delay ART. In this study, those who initiated ART had a 96% reduction in HIV transmission to the uninfected partners.[3] Almost all of the participants were in heterosexual relationships, all participants received risk-reduction counseling, and the absolute number of transmission events was low: 1 among ART initiators and 27 among ART delayers. Over the course of the study virologic failure rates were less than 5%, a value much lower than generally seen in individuals taking ART for their own health. These low virologic failure rates suggest high levels of adherence to ART in the study, which may have been facilitated by the frequency of study follow-up (study visits were monthly) and by participants' sense of obligation to protect their uninfected partners. Therefore, caution is indicated when interpreting the extent to which ART for the HIV-infected partner protects seronegative partners in contexts where adherence and, thus, rates of continuous viral suppression, may be lower. Furthermore, for HIV-infected MSM and IDUs, biological and observational data suggest suppressive ART also should protect against transmission, but the actual extent of protection has not been established.

Rates of HIV risk behaviors can increase coincidently with the availability of potent combination ART, in some cases almost doubling compared with rates in the era prior to highly effective therapy.[9] A meta-analysis demonstrated that the prevalence of unprotected sex acts was increased in HIV-infected individuals who believed that receiving ART or having a suppressed viral load protected against transmitting HIV.[41] Attitudinal shifts away from safer sexual practices since the availability of potent ART underscore the role of provider-initiated HIV prevention counseling. With wider recognition that effective treatment decreases the risk of HIV transmission, it is particularly important for providers to help patients understand that a sustained viral load below the limits of detection will dramatically reduce but does not absolutely assure the absence of HIV in the genital and blood compartments and, hence, the inability to transmit HIV to others.[41-42]

Maximal suppression of viremia not only depends on the potency of the ARV regimen used but also on the patient's adherence to prescribed therapy. Suboptimal adherence can lead to viremia that not only harms the patient but also increases his/her risk of transmitting HIV (including drug-resistant strains) via sex or needle sharing. Screening for and treating behavioral conditions that can impact adherence, such as depression and alcohol and substance use, improve overall health and reduce the risk of secondary transmission.

Summary

Consistent and effective use of ART resulting in a sustained reduction in viral load in conjunction with consistent condom usage, safer sex and drug use practices, and detection and treatment of STDs are essential

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tools for prevention of sexual and blood-borne transmission of HIV. Given these important considerations, medical visits provide a vital opportunity to reinforce HIV prevention messages, discuss sex- and drug-related risk behaviors, diagnose and treat intercurrent STDs, review the importance of medication adherence, and foster open communication between provider and patient.

References

1. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. *PLoS One*. 2011;6(8):e17502.
2. Centers for Disease Control and Prevention. HIV Surveillance Report http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. 2009. Published February 2011. Accessed December 7, 2011.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505.
4. Mayer KH, Safren SA, Gordon CM. HIV care providers and prevention: opportunities and challenges. *J Acquir Immune Defic Syndr*. Oct 1 2004;37(Suppl 2):S130-132.
5. Morin SF, Koester KA, Steward WT, et al. Missed opportunities: prevention with HIV-infected patients in clinical care settings. *J Acquir Immune Defic Syndr*. Aug 1 2004;36(4):960-966.
6. Metsch LR, McCoy CB, Miles CC, Wohler B. Prevention myths and HIV risk reduction by active drug users. *AIDS Educ Prev*. Apr 2004;16(2):150-159.
7. Johnson WD, Diaz RM, Flanders WD, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *Cochrane Database Syst Rev*. 2008(3):CD001230.
8. Centers for Disease Control and Prevention (CDC). Evolution of HIV/AIDS prevention programs—United States, 1981-2006. *MMWR Morb Mortal Wkly Rep*. Jun 2 2006;55(21):597-603.
9. Gorbach PM, Drumright LN, Daar ES, Little SJ. Transmission behaviors of recently HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr*. May 2006;42(1):80-85.
10. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. Dec 17 2010;59(RR-12):1-110.
11. Tanton C, Weiss HA, Le Goff J, et al. Correlates of HIV-1 genital shedding in Tanzanian women. *PLoS One*. 2011;6(3):e17480.
12. Wright TC, Jr., Subbarao S, Ellerbrock TV, et al. Human immunodeficiency virus 1 expression in the female genital tract in association with cervical inflammation and ulceration. *Am J Obstet Gynecol*. Feb 2001;184(3):279-285.
13. Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA*. Jul 1 1998;280(1):61-66.
14. Celentano DD, Latimore AD, Mehta SH. Variations in sexual risks in drug users: emerging themes in a behavioral context. *Curr HIV/AIDS Rep*. Nov 2008;5(4):212-218.
15. Mitchell MM, Latimer WW. Unprotected casual sex and perceived risk of contracting HIV among drug users in Baltimore, Maryland: evaluating the influence of non-injection versus injection drug user status. *AIDS Care*. Feb 2009;21(2):221-230.
16. Colfax G, Coates TJ, Husnik MJ, et al. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health*. Mar 2005;82(1 Suppl 1):i62-70.
17. Mimiaga MJ, Reisner SL, Fontaine YM, et al. Walking the line: stimulant use during sex and HIV risk behavior among Black urban MSM. *Drug Alcohol Depend*. Jul 1 2010;110(1-2):30-37.

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18. Ostrow DG, Plankey MW, Cox C, et al. Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS. *J Acquir Immune Defic Syndr*. Jul 1 2009;51(3):349-355.
19. Sterk CE, Theall KP, Elifson KW. Who's getting the message? Intervention response rates among women who inject drugs and/or smoke crack cocaine. *Prev Med*. Aug 2003;37(2):119-128.
20. Sterk CE, Theall KP, Elifson KW, Kidder D. HIV risk reduction among African-American women who inject drugs: a randomized controlled trial. *AIDS Behav*. Mar 2003;7(1):73-86.
21. Strathdee SA, Sherman SG. The role of sexual transmission of HIV infection among injection and non-injection drug users. *J Urban Health*. Dec 2003;80(4 Suppl 3):iii7-14.
22. Copenhaver MM, Johnson BT, Lee IC, Harman JJ, Carey MP. Behavioral HIV risk reduction among people who inject drugs: meta-analytic evidence of efficacy. *J Subst Abuse Treat*. Sep 2006;31(2):163-171.
23. Hartel DM, Schoenbaum EE. Methadone treatment protects against HIV infection: two decades of experience in the Bronx, New York City. *Public Health Rep*. Jun 1998;113(Suppl 1):107-115.
24. Metzger DS, Navaline H, Woody GE. Drug abuse treatment as AIDS prevention. *Public Health Rep*. Jun 1998;113(Suppl 1):97-106.
25. Crawford ND, Vlahov D. Progress in HIV reduction and prevention among injection and noninjection drug users. *J Acquir Immune Defic Syndr*. Dec 2010;55(Suppl 2):S84-87.
26. Shoptaw S, Heinzerling KG, Rotheram-Fuller E, et al. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. Aug 1 2008;96(3):222-232.
27. Heinzerling KG, Swanson AN, Kim S, et al. Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend.* Jun 1 2010;109(1-3):20-29.
28. Centers for Disease Control and Prevention. Methamphetamine Use and Risk for HIV/AIDS. Atlanta, GA: Centers for Disease Control and Prevention, US Dept. of Health and Human Services. Last Modified: May 3, 2007.
29. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med*. Apr 6 2011;3(77):77ra29.
30. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS*. Sep 24 2009;23(15):2050-2054.
31. Graham SM, Holte SE, Peshu NM, et al. Initiation of antiretroviral therapy leads to a rapid decline in cervical and vaginal HIV-1 shedding. *AIDS*. Feb 19 2007;21(4):501-507.
32. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS*. Jan 28 2000;14(2):117-121.
33. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of Per-Coital-Act HIV-1 Infectivity Among African HIV-1-Serodiscordant Couples. *J Infect Dis*. Feb 2012;205(3):358-365.
34. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. Mar 30 2000;342(13):921-929.
35. Das M, Chu PL, Santos GM, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One*. 2010;5(6):e11068.
36. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet*. Aug 14 2010;376(9740):532-539.
37. Porco TC, Martin JN, Page-Shafer KA, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. *AIDS*. Jan 2 2004;18(1):81-88.
38. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS*. Jul 17 2009;23(11):1397-1404.

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39. Cu-Uvin S, DeLong AK, Venkatesh KK, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. Oct 23 2010;24(16):2489-2497.

40. Sturmer M, Doerr HW, Berger A, Gute P. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? *Antivir Ther*. 2008;13(5):729-732.

41. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA*. Jul 14 2004;292(2):224-236.

42. Rice E, Batterham P, Rotheram-Borus MJ. Unprotected sex among youth living with HIV before and after the advent of highly active antiretroviral therapy. *Perspect Sex Reprod Health*. Sep 2006;38(3):162-167.

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

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

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

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

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Appendix A: Key to Acronyms (Last updated July 14, 2016; last reviewed July 14, 2016)

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonavir
COBI or c	cobicistat
d4T	stavudine
DCV	daclatasvir
ddC	zalcitabine
ddI	didanosine
DLV	delavirdine
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
EFV/c/TDF/FTC	efavirenz/cobicistat/tenofovir disoproxil fumarate/emtricitabine
ETR	etravirine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat
EVG/c/TAF/FTC	elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine
EVG/c/TDF/FTC	elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine
EVG/r	elvitegravir/ritonavir
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine
IDV	indinavir
IDV/r	indinavir/ritonavir
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor

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RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
SQV	saquinavir
SQV/r	saquinavir/ritonavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
TPV/r	tipranavir/ritonavir
ZDV	zidovudine

General Terms

Abbreviation	**Definition**
17-BMP	beclomethasone 17-monopropionate
Al	aluminum
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AWP	average wholesale price
BID	twice daily
BMD	bone mineral density
Ca	calcium
$CaCO_3$	calcium carbonate
CCB	calcium channel blockers
CD4	CD4 T lymphocyte
CKD	chronic kidney disease
Cl	chloride
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CrCl	creatinine clearance
CVD	cardiovascular disease
CYP	cytochrome P
DAAs	direct-acting antivirals
DHA	dihydroartemisinin

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DMPA	depot medroxyprogesterone acetate
EC	enteric coated
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EI	entry inhibitor
FDA	Food and Drug Administration
Fe	iron
GAZT	azidothymidine glucuronide
GI	gastrointestinal
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCO3	bicarbonate
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HLA	human leukocyte antigen
HMG-CoA	hydroxy-methylglutaryl-coenzyme A
HSR	hypersensitivity reaction
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
K	potassium
LDL	low-density lipoprotein
MATE	multidrug and toxin extrusion transporter
Mg	magnesium
MI	myocardial infarction
MPA	medroxyprogesterone acetate
N/A	Not Applicable
Na	Sodium
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OCT2	organic cation transporter 2
OH-itraconazole	active metabolite of itraconazole
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jiroveci* pneumonia
PDE5	phosphodiesterase type 5
PI	protease inhibitor
PPI	proton pump inhibitor
PK	pharmacokinetic

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PO	orally
PPI	Proton pump inhibitor
q(n)d	every (n) days
q(n)h	every (n) hours
QTc	QT corrected for heart rate
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SSRI	selective serotonin reuptake inhibitor
STR	single-table regimen
TB	tuberculosis
TCA	tricyclic anti-depressant
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
UGT1A1	uridine diphosphate glucuronosyltransferase
VPA	valproic acid
WHO	World Health Organization
XR	extended release
Zn	Zinc

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Abacavir (ABC) *Ziagen* **Note:** Generic available in tablet formulation **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Ziagen: • 300 mg tablet • 20 mg/mL oral solution	Ziagen: • 300 mg BID, *or* • 600 mg once daily • Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites: 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 7).	1.5 hours/ 12–26 hours	• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. • For patients with history of HSR, re-challenge is not recommended. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir (ABC/ZDV/3TC) **Note:** Generic available	Trizivir: • (ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg) tablet	Trizivir: • 1 tablet BID			
Epzicom (ABC/3TC)	Epzicom: • (ABC 600 mg plus 3TC 300 mg) tablet	Epzicom: • 1 tablet once daily			
Triumeq (ABC/3TC/DTG)	Triumeq: • (ABC 600 mg plus 3TC 300 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Didanosine (ddI) *Videx* *Videx EC* **Note:** Generic available; dose same as Videx or Videx EC	Videx EC: • 125, 200, 250, and 400 mg capsules Videx: • 10 mg/mL oral solution	Body Weight ≥60 kg: • 400 mg once daily *With TDF:* • 250 mg once daily Body Weight <60 kg: • 250 mg once daily *With TDF:* • 200 mg once daily Take 1/2 hour before or 2 hours after a meal. **Note:** Preferred dosing with oral solution is BID (total daily dose divided into 2 doses).	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1.5 hours/ >20 hours	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis with or without pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with non-cirrhotic portal hypertension; in some cases, patients presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Emtricitabine (FTC) *Emtriva* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Emtriva: • 200 mg hard gelatin capsule • 10 mg/mL oral solution	Emtriva: *Capsule:* • 200 mg once daily *Oral Solution:* • 240 mg (24 mL) once daily Take without regard to meals.	Renal excretion: 86% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	10 hours/ >20 hours	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla (FTC/EFV/TDF)	Atripla: • (FTC 200 mg plus EFV 600 mg plus TDF 300 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (FTC/RPV/TDF)	Complera: • (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet	Complera: • 1 tablet once daily with a meal			
Descovy (FTC/TAF)	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (FTC/EVG/c/TAF)	Genvoya: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (FTC/RPV/TAF)	Odefsey: • (FTC 200 mg plus RPV 25 mg plus TAF 25 mg) tablet	Odefsey: • 1 tablet once daily with a meal			
Stribild (FTC/EVG/c/TDF)	Stribild: • (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food			
Truvada (FTC/TDF)	Truvada: • (FTC 200 mg plus TDF 300 mg) tablet	Truvada: • 1 tablet once daily			

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Lamivudine (3TC) *Epivir* **Note:** Generic available **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Epivir: • 150 and 300 mg tablets • 10 mg/mL oral solution	Epivir: • 150 mg BID, *or* • 300 mg once daily • Take without regard to meals.	Renal excretion: 70% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	5–7 hours/ 18–22 hours	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir (3TC/ZDV) **Note:** Generic available	Combivir: • (3TC 150 mg plus ZDV 300 mg) tablet	Combivir: • 1 tablet BID			
Epzicom (3TC/ABC)	Epzicom: • (3TC 300 mg plus ABC 600 mg) tablet	Epzicom: • 1 tablet once daily			
Trizivir (3TC/ZDV/ABC) **Note:** Generic available	Trizivir: • (3TC 150 mg plus ZDV 300 mg plus ABC 300 mg) tablet	Trizivir: • 1 tablet BID			
Triumeq (3TC/ABC/DTG)	Triumeq: • (3TC 300 mg plus ABC 600 mg plus DTG 50 mg) tablet	Triumeq: • 1 tablet once daily			
Stavudine (d4T) *Zerit* **Note:** Generic available	Zerit: • 15, 20, 30, and 40 mg capsules • 1 mg/mL oral solution	Body Weight ≥60 kg: • 40 mg BID Body Weight <60 kg: • 30 mg BID Take without regard to meals. **Note:** WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion: 50% Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	1 hour/7.5 hours	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Tenofovir Alafenamide (TAF) **Only available as a component of fixed-dose combinations (by trade name and abbreviation):**	See fixed-dose combinations below.	See fixed-dose combinations below.	Metabolized by cathepsin A; P-glycoprotein substrate Not recommended in patients with CrCl < 30 mL/min (see Appendix B, Table 7).	0.5 hours/150–180 hours	• Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy; less likely than from TDF • Osteomalacia, decrease in bone mineral density; lesser effect than from TDF • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TAF. • Diarrhea, nausea, headache
Descovy (TAF/FTC)	Descovy: • (FTC 200 mg plus TAF 25 mg) tablet	Descovy: • 1 tablet once daily			
Genvoya (TAF/EVG/c/FTC)	Genvoya: • (TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet	Genvoya: • 1 tablet once daily with food			
Odefsey (TAF/RPV/FTC)	Odefsey: • (TAF 25 mg plus RPV 25 mg plus FTC 200 mg) tablet	Odefsey: • 1 tablet once daily with a meal			

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination**	**Serum/ Intracellular Half-Lives**	**Adverse Events**[b]
Tenofovir Disoproxil Fumarate (TDF) *Viread* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Viread: • 150, 200, 250, and 300 mg tablets • 40 mg/g oral powder	Viread: • 300 mg once daily, *or* • 7.5 level scoops once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1 g of oral powder). • Take without regard to meals. 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.**	Renal excretion is primary route of elimination. Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	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 HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla (TDF/EFV/FTC)	Atripla: • (TDF 300 mg plus EFV 600 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet at or before bedtime • Take on an empty stomach to reduce side effects.			
Complera (TDF/RPV/FTC)	Complera: • (TDF 300 mg plus RPV 25 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Stribild (TDF/EVG/c/FTC)	Stribild: • (TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet	Stribild: • 1 tablet once daily • Take with food.			
Truvada (TDF/FTC)	Truvada: • (TDF 300 mg plus FTC 200 mg) tablet	Truvada: • 1 tablet once daily • Take without regard to meals.			

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Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination	Serum/ Intracellular Half-Lives	Adverse Events[b]
Zidovudine (ZDV) *Retrovir* **Note:** Generic available **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Retrovir: • 100 mg capsule • 300 mg tablet (only available as generic) • 10 mg/mL intravenous solution • 10 mg/mL oral solution	Retrovir: • 300 mg BID, *or* • 200 mg TID • Take without regard to meals.	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7).	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 (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir (ZDV/3TC) **Note:** Generic available	Combivir: • (ZDV 300 mg plus 3TC 150 mg) tablet	Combivir: • 1 tablet BID • Take without regard to meals.			
Trizivir (ZDV/3TC/ABC) **Note:** Generic available	Trizivir: • (ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg) tablet	Trizivir: • 1 tablet BID • Take without regard to meals.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; BID = twice daily; c, COBI = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine

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Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

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

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum Half-Life**	**Adverse Events**[b]
Efavirenz (EFV) *Sustiva* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	Sustiva: • 50 and 200 mg capsules • 600 mg tablet	Sustiva: • 600 mg once daily, at or before bedtime • Take on an empty stomach to reduce side effects.	Metabolized by CYPs 2B6 (primary), 3A4, and 2A6 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer	40–55 hours	• Rash[c] • Neuropsychiatric symptoms[d] • Increased transaminase levels • Hyperlipidemia • False-positive results with some cannabinoid and benzodiazepine screening assays reported. • Teratogenic in non-human primates and potentially teratogenic during the first trimester of pregnancy in humans
Atripla (EFV/TDF/FTC)	Atripla: • (EFV 600 mg plus TDF 300 mg plus FTC 200 mg) tablet	Atripla: • 1 tablet once daily, at or before bedtime			
Etravirine (ETR) *Intelence*	• 25, 100, and 200 mg tablets	• 200 mg BID • Take following a meal.	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 hours	• Rash, including Stevens-Johnson syndrome[c] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported. • Nausea

Nevirapine (NVP) *Viramune or Viramine XR*
Generic available for 200 mg tablets and oral suspension
	• 200 mg tablet
	• 400 mg XR tablet
	• 50 mg/5 mL oral suspension
		• 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily
		• Take without regard to meals.
		• Repeat lead-in period if therapy is discontinued for >7 days.
		• In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves but not longer than 28 days total.
			CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hours	• Rash, including Stevens-Johnson syndrome[c]
					• Symptomatic hepatitis, including fatal hepatic necrosis, has been reported:
					  • Rash reported in approximately 50% of cases.
					  • Occurs at 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.

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Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

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

Generic Name (Abbreviation) *Trade Name*	**Formulations**	**Dosing Recommendations**[a]	**Elimination/ Metabolic Pathway**	**Serum/ Half-Life**	**Adverse Events**[b]
Rilpivirine (RPV) *Edurant* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	Edurant: • 25 mg tablet	Edurant: • 25 mg once daily • Take with a meal.	CYP3A4 substrate	50 hours	• Rash[c] • Depression, insomnia, headache • Hepatotoxicity
Complera (RPV/TDF/FTC)	Complera: • (RPV 25 mg plus TDF 300 mg plus FTC 200 mg) tablet	Complera: • 1 tablet once daily • Take with a meal.			
Odefsey (RPV/TAF/FTC)	Odefsey: • (RPV 25 mg plus TAF 25 mg plus FTC 200 mg) tablet	Odefsey: • 1 tablet once daily • Take with a meal.			

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

[c] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[d] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Key to Abbreviations: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release

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Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 1 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Atazanavir (ATV) *Reyataz* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	Reyataz: • 100, 150, 200, and 300 mg capsules • 50 mg single packet oral powder	In ARV-Naive Patients: • (ATV 300 mg plus RTV 100 mg) once daily; *or* • ATV 400 mg once daily With TDF or in ARV-Experienced Patients: • (ATV 300 mg plus RTV 100 mg) once daily With EFV in ARV-Naive Patients: • (ATV 400 mg plus RTV 100 mg) once daily Take with food. For recommendations on dosing with H2 antagonists and PPIs, refer to Table 19a.	CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7 hours	Room temperature (up to 25º C or 77º F)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Cholelithiasis • Nephrolithiasis • Renal insufficiency • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting) • Skin rash • Increase in serum creatinine (with COBI)
Evotaz (ATV/c)	Evotaz: • (ATV 300 mg plus COBI 150 mg) tablet	Evotaz: • 1 tablet once daily • Take with food. With TDF: • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	ATV: as above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			
Darunavir (DRV) *Prezista* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	• 75, 150, 600, and 800 mg tablets • 100 mg/mL oral suspension	In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations: • (DRV 800 mg plus RTV 100 mg) once daily In ARV-Experienced Patients with One or More DRV Resistance Mutations: • (DRV 600 mg plus RTV 100 mg) BID Unboosted DRV **is not recommended**. Take with food.	CYP3A4 inhibitor and substrate CYP2C9 inducer	15 hours (when combined with RTV)	Room temperature (up to 25º C or 77º F)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Increase in serum creatinine (with COBI)
Prezcobix (DRV/c)	Prezcobix: • (DRV 800 mg plus COBI 150 mg) tablet	Prezcobix: • 1 tablet once daily • Take with food. **Not recommended** for patients with one or more DRV resistance-associated mutations. With TDF: • **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).	DRV: As above COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor			

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Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 2 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Fosamprenavir (FPV) *Lexiva* (a prodrug of APV)	• 700 mg tablet • 50 mg/mL oral suspension	In ARV-Naive Patients: • FPV 1400 mg BID, *or* • (FPV 1400 mg plus RTV 100–200 mg) once daily, *or* • (FPV 700 mg plus RTV 100 mg) BID In PI-Experienced Patients (**Once-Daily Dosing Not Recommended**): • (FPV 700 mg plus RTV 100 mg) BID With EFV: • (FPV 700 mg plus RTV 100 mg) BID, *or* • (FPV 1400 mg plus RTV 300 mg) once daily *Tablet:* • Without RTV tablet: Take without regard to meals. • With RTV tablet: Take with meals. *Oral Suspension:* • Take without food.	APV is a CYP3A4 substrate, inhibitor, and inducer. Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	7.7 hours (APV)	Room temperature (up to 25º C or 77º F)	• Skin rash (12% to 19%): FPV has a sulfonamide moiety. • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV) *Crixivan*	• 100, 200, and 400 mg capsules	• 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) BID • Take without regard to meals.	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7).	1.5–2 hours	Room temperature (15º to 30º C or 59º to 86º F) Protect from moisture.	• 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 increased bleeding episodes in patients with hemophilia

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Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 3 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Lopinavir/ Ritonavir (LPV/r) *Kaletra*	Tablets: • (LPV 200 mg plus RTV 50 mg), *or* • (LPV 100 mg plus RTV 25 mg) Oral Solution: • Each 5 mL contains (LPV 400 mg plus RTV 100 mg). • Oral solution contains 42% alcohol.	• (LPV 400 mg plus RTV 100 mg) BID, *or* • (LPV 800 mg plus RTV 200 mg) once daily Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-Naive or PI-Experienced Patients): • LPV/r 500 mg/125 mg tablets BID (use a combination of 2 LPV/r 200 mg/50 mg tablets plus 1 LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or* • LPV/r 520 mg/130 mg oral solution BID *Tablet:* • Take without regard to meals. *Oral Solution:* • Take with food.	CYP3A4 inhibitor and substrate	5–6 hours	Oral tablet is stable at room temperature. Oral solution is stable at 2° to 8° C (36° to 46° F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25º C or 77º F).	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased 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*	• 250 and 625 mg tablets • 50 mg/g oral powder	• 1250 mg BID, *or* • 750 mg TID Dissolve tablets in a small amount of water, mix admixture well, and consume immediately. Take with food.	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor	3.5–5 hours	Room temperature (15º to 30º C or 59º to 86º F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation
Ritonavir (RTV) *Norvir* **Also available as a component of fixed-dose combination (see Lopinavir/ Ritonavir)**	• 100 mg tablet • 100 mg soft gel capsule • 80 mg/mL oral solution Oral solution contains 43% alcohol.	As Pharmacokinetic Booster (or Enhancer) for Other PIs: • 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations). *Tablet:* • Take with food. *Capsule and Oral Solution:* • To improve tolerability, take with food if possible.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor; Inducer of CYPs 1A2, 2C8, 2C9, and 2C19 and UGT1A1	3–5 hours	Tablets do not require refrigeration. Refrigerate capsules. Capsules can be left at room temperature (up to 25º C or 77º F) for up to 30 days. **Oral solution should not be refrigerated.**	• GI intolerance, nausea, vomiting, diarrhea • Paresthesia (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

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Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 4 of 4)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathway	Serum Half-Life	Storage	Adverse Events[b]
Saquinavir (SQV) *Invirase*	• 500 mg tablet • 200 mg capsule	• (SQV 1000 mg plus RTV 100 mg) BID • Unboosted SQV **is not recommended**. • Take with meals or within 2 hours after a meal.	CYP3A4 substrate	1–2 hours	Room temperature (15º to 30º C or 59º to 86º F)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV.
Tipranavir (TPV) *Aptivus*	• 250 mg capsule • 100 mg/mL oral solution	• (TPV 500 mg plus RTV 200 mg) BID Unboosted TPV **is not recommended**. With RTV Tablets: • Take with meals. With RTV Capsules or Solution: • Take without regard to meals.	CYP P450 3A4 inducer and substrate CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer Net effect when combined with RTV (CYP3A4, 2D6 inhibitor)	6 hours after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25º C or 77º F) for up to 60 days. **Oral solution should not be refrigerated or frozen** and should be used within 60 days after bottle is opened.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases. • Skin rash (3% to 21%): 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 anti-coagulant or anti-platelet agents (including vitamin E). • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; 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; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir

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Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)

Generic Name (Abbreviation) *Trade Name*	Formulations	Dosing Recommendations[a]	Elimination/ Metabolic Pathways	Serum Half-Life	Adverse Events[b]
Dolutegravir (DTG) *Tivicay* **Also available as a component of fixed-dose combination (by trade name and abbreviation):**	• 50 mg tablet	ARV-Naive or ARV-Experienced, INSTI-Naive Patients: • 50 mg once daily ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Co-Administered with EFV, FPV/r, TPV/r, or Rifampin: • 50 mg BID INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance: • 50 mg BID Take without regard to meals.	UGT1A1 mediated glucuronidation Minor contribution from CYP3A4	~14 hours	• HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported. • Insomnia • Headache • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Triumeq (DTG/ABC/3TC)	Triumeq: • (DTG 50 mg plus ABC 600 mg plus 3TC 300 mg) tablet	Triumeq: • Take 1 tablet daily without regard to meals.			
Elvitegravir (EVG) *Vitekta* **Also available as a component of fixed-dose combinations (by trade name and abbreviation):**	• 85 and 150 mg tablets	With Once Daily ATV/r or BID LPV/r: • 85 mg once daily with food With BID DRV/r, FPV/r, or TPV/r: • 150 mg once daily with food Unboosted EVG **is not recommended**.	CYP3A, UGT1A1/3 substrate	~9 hours	• Nausea • Diarrhea • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)
Genvoya (EVG/c/FTC/TAF)	Genvoya: • (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg) tablet	Genvoya: • 1 tablet once daily with food **Not recommended** for patients with CrCl <30 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**	EVG: As above COBI: CYP3A, CYP2D6 (minor); CYP3A inhibitor	~13 hours	
Stribild (EVG/c/FTC/ TDF)	Stribild: • (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg) tablet	Stribild: • 1 tablet once daily with food **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B Table 7 for the equation for calculating CrCl). **Not recommended for use with other ARV drugs.**		~13 hours	

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Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (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*	• 400 mg tablet • 25 and 100 mg chewable tablets • 100 mg single packet for oral suspension	• 400 mg BID With Rifampin: • 800 mg BID Take without regard to meals.	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 in patients with pre-existing psychiatric conditions)

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BID = twice daily; c, COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DRV/r = darunavir/ritonavir; DTG = dolutegravirEFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate gluconyltransferase

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed April 8, 2015)

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendation	Serum Half-Life	Elimination	Storage	Adverse Events[a]
Enfuvirtide (T20) *Fuzeon*	• Injectable; supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	• 90 mg (1 mL) subcutaneously BID	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25° C or 77° F). Re-constituted solution should be refrigerated at 2° to 8° C (36° to 46° F) and used within 24 hours.	• 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 (<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 14.

Key to Abbreviations: BID = twice daily; HSR = hypersensitivity reaction; T20 = enfuvirtide

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Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed April 8, 2015)

Generic Name (Abbreviation)/ *Trade Name*	Formulation	Dosing Recommendations[a]	Serum Half-Life	Elimination/ Metabolic Pathway	Adverse Events[b]
Maraviroc (MVC) *Selzentry*	• 150 and 300 mg tablets	• **150 mg BID** when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) • Take 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 dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

Key to Abbreviations: BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T20 = enfuvirtide; TPV/r = tipranavir/ritonavir

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)

See the reference section at the end of this table for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NRTIs Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Epzicom, Stribild, Triumeq, or Trizivir. Use of Truvada is not recommended in patients with CrCl <30 mL/min.			
Abacavir (ABC) *Ziagen*	• 300 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A: • 200 mg PO BID (use oral solution) Child-Pugh Class B or C: • Contraindicated
Didanosine EC (ddI) *Videx EC*	Body Weight ≥60 kg: • 400 mg PO once daily Body Weight <60 kg: • 250 mg PO once daily	**Dose (Once Daily)** **CrCl (mL/min) / ≥60 kg / <60 kg** 30–59: 200 mg / 125 mg 10–29: 125 mg / 125 mg <10, HD[c], CAPD: 125 mg / 75 mg oral solution	No dosage adjustment necessary
Didanosine Oral Solution (ddI) *Videx*	Body Weight ≥60 kg: • 200 mg PO BID, *or* • 400 mg PO once daily Body Weight <60 kg: • 250 mg PO once daily, *or* • 125 mg PO BID	**Dose (Once Daily)** **CrCl (mL/min) / ≥60 kg / <60 kg** 30–59: 200 mg / 150 mg 10–29: 150 mg / 100 mg <10, HD[c], CAPD: 100 mg / 75 mg	No dosage adjustment necessary
Emtricitabine (FTC) *Emtriva*	• 200 mg oral capsule once daily, *or* • 240 mg (24 mL) oral solution once daily	**Dose** **CrCl (mL/min) / Capsule / Solution** 30–49: 200 mg q48h / 120 mg q24h 15–29: 200 mg q72h / 80 mg q24h <15 or on HD[c]: 200 mg q96h / 60 mg q24h	No dosage recommendation
Lamivudine (3TC) *Epivir*	• 300 mg PO once daily, *or* • 150 mg PO BID	**CrCl (mL/min) / Dose** 30–49: 150 mg q24h 15–29: 1 x 150 mg, then 100 mg q24h 5–14: 1 x 150 mg, then 50 mg q24h <5 or on HD[c]: 1 x 50 mg, then 25 mg q24h	No dosage adjustment necessary

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NRTIs, continued			
Stavudine (d4T) *Zerit*	Body Weight ≥60 kg: • 40 mg PO BID Body Weight <60 kg: • 30 mg PO BID	Dose CrCl (mL/min) / ≥60 kg / <60 kg 26–50 / 20 mg q12h / 15 mg q12h 10–25 or on HD[c] / 20 mg q24h / 15 mg q24h	No dosage recommendation
Tenofovir Alafenamide/ Emtricitabine (TAF/FTC) *Descovy*	TAF only available as a component of fixed-dose combinations (i.e., *Descovy*, *Genvoya*, and *Odefsey*) • TAF 10 mg PO daily with EVG/c (*Genvoya*), *or* • TAF 25 mg PO daily in other FDCs	CrCl (mL/min) / Dose <30 or on HD[c] / Not recommended	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Tenofovir Disoproxil Fumarate (TDF) *Viread*	• 300 mg PO once daily	CrCl (mL/min) / Dose 30–49 / 300 mg q48h 10–29 / 300 mg twice weekly (every 72–96 hours) <10 and not on HD / No recommendation On HD[c] / 300 mg q7d	No dosage adjustment necessary
Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) *Truvada*	• 1 tablet PO once daily	CrCl (mL/min) / Dose 30–49 / 1 tablet q48h <30 or on HD / Not recommended	No dosage recommendation
Zidovudine (AZT, ZDV) *Retrovir*	• 300 mg PO BID	CrCl (mL/min) / Dose <15 or on HD[c] / 100 mg TID or 300 mg once daily	No dosage recommendation
NNRTIs			
Delavirdine (DLV) *Rescriptor*	• 400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) *Sustiva*	• 600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EFV/TDF/FTC) *Atripla*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
NNRTIs, continued			
Etravirine (ETR) *Intelence*	• 200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Nevirapine (NVP) *Viramune* or *Viramune XR*	• 200 mg PO BID, *or* • 400 mg PO once daily (using Viramune XR formulation)	Patients on HD: • Limited data; no dosage recommendation	Child-Pugh Class A: • No dosage adjustment Child-Pugh Class B or C: • Contraindicated
Rilpivirine (RPV) *Edurant*	• 25 mg PO once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/Tenofovir Alafenamide/ Emtricitabine (RPV/TAF/FTC) *Odefsey*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <30 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine (RPV/TDF/FTC) *Complera*	• 1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • No dosage recommendation
PIs			
Atazanavir (ATV) *Reyataz*	• 400 mg PO once daily, *or* • (ATV 300 mg plus RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction who do not require HD. ARV-Naive Patients on HD: • (ATV 300 mg plus RTV 100 mg) once daily ARV-Experienced Patients on HD: • ATV or ATV/r not recommended	Child-Pugh Class B: • 300 mg once daily Child-Pugh Class C: • Not recommended RTV boosting **is not recommended** in patients with hepatic impairment.
Atazanavir/ Cobicistat (ATV/c) *Evotaz*	• 1 tablet PO once daily	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	Not recommended in patients with hepatic impairment

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Darunavir (DRV) *Prezista*	ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations: • (DRV 800 mg plus RTV 100 mg) PO once daily ARV-Experienced Patients with at Least One DRV Resistance Mutation: • (DRV 600 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • No dosage adjustment Severe Hepatic Impairment: • Not recommended
Darunavir/ Cobicistat (DRV/c) *Prezcobix*	• 1 tablet PO once daily (only recommended for patients without DRV-associated resistance mutations)	If Used with TDF: • Not recommended for use in patients with CrCl <70 mL/min	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Fosamprenavir (FPV) *Lexiva*	• 1400 mg PO BID, *or* • (FPV 1400 mg plus RTV 100–200 mg) PO once daily, *or* • (FPV 700 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	PI-Naive Patients Only *Child-Pugh Score 5–9:* • 700 mg BID *Child-Pugh Score 10–15:* • 350 mg BID PI-Naive or PI-Experienced Patients *Child-Pugh Score 5–6:* • (700 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 7–9:* • (450 mg BID plus RTV 100 mg) once daily *Child-Pugh Score 10–15:* • (300 mg BID plus RTV 100 mg) once daily
Indinavir (IDV) *Crixivan*	• 800 mg PO q8h	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency Because of Cirrhosis: • 600 mg q8h

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
PIs, continued			
Lopinavir/Ritonavir (LPV/r) *Kaletra*	• (LPV 400 mg plus RTV 100 mg) PO BID, *or* • (LPV 800 mg plus RTV 200 mg) PO once daily	Avoid once-daily dosing in patients on HD.	No dosage recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV) *Viracept*	• 1250 mg PO BID	No dosage adjustment necessary	Mild Hepatic Impairment: • No dosage adjustment Moderate-to-Severe Hepatic Impairment: • Do not use.
Ritonavir (RTV) *Norvir*	As a PI-Boosting Agent: • 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV) *Invirase*	• (SQV 1000 mg plus RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Impairment: • Use with caution. Severe Hepatic Impairment: • Contraindicated
Tipranavir (TPV) *Aptivus*	• (TPV 500 mg plus RTV 200 mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: • Use with caution. Child-Pugh Class B or C: • Contraindicated
INSTIs			
Dolutegravir (DTG) *Tivicay*	• 50 mg once daily, *or* • 50 mg BID	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir (EVG) *Vitekta*	• 85 mg or 150 mg[a] once daily	No dosage adjustment necessary	Child-Pugh Class A or B: • No dosage adjustment Child-Pugh Class C: • Not recommended
Elvitegravir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine (EVG/c/TAF/FTC) *Genvoya*	• 1 tablet once daily	Not recommended for use in patients with CrCl <30 mL/min	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended

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Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)

ARVs Generic Name (Abbreviation) *Trade Name*	Usual Daily Dose[a]	Dosing in Renal Insufficiency[b]	Dosing in Hepatic Impairment
INSTIs, continued			
Elvitegravir/ Cobicistat/ Tenofovir Disoproxil Fumarate/ Emtricitabine (EVG/c/TDF/FTC) *Stribild*	• 1 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.	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • Not recommended
Raltegravir (RAL) *Isentress*	• 400 mg BID	No dosage adjustment necessary	Mild-to-Moderate Hepatic Insufficiency: • No dosage adjustment necessary Severe Hepatic Insufficiency: • No recommendation
Fusion Inhibitor			
Enfuvirtide (T20) *Fuzeon*	• 90 mg subcutaneous BID	No dosage adjustment necessary	No dosage 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 6 for detailed dosing information.	CrCl <30 mL/min or on HD *Without Potent CYP3A Inhibitors or Inducers:* • 300 mg BID; reduce to 150 mg BID if postural hypotension occurs *With Potent CYP3A Inducers or Inhibitors:* • Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

[a] Refer to Appendix B, Tables 1–6 for additional dosing information.

[b] Including with chronic ambulatory peritoneal dialysis and hemodialysis.

[c] On dialysis days, take dose after HD session.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AZT = zidovudine; BID = twice daily; c, COBI = cobicistat; CAPD = chronic ambulatory peritoneal dialysis; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IDV = indinavir; 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; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZVD = zidovudine

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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 µmol/L to 50 µmol/L)	>3 mg/dL (>50 µmol/L)
Modified total bilirubin[b]	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

[a] Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Child-Pugh Score[a]
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

[a] Sum of points for each component of the Child-Pugh Score

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