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

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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)

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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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:
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 virologic suppression 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. 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, rilpivirine (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 (AI)
- DTG plus either TDF/FTC (AI) or TAF/FTC (AII)
- EVG/c/TAF/FTC (AI) or EVG/c/TDF/FTC (AI)
- RAL plus either TDF/FTC (AI) or TAF/FTC (AII)

#### Boosted PI plus 2 NRTIs:
- DRV/r plus either TDF/FTC (AI) or TAF/FTC (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 (BI)
- EFV plus TAF/FTC (BII)
- RPV/TDF/FTC (BI) or RPV/TAF/FTC (BII) if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm³

#### Boosted PI plus 2 NRTIs:
- (ATV/c or ATV/r) plus either TDF/FTC (BI) or TAF/FTC (BII)
- DRV/c (BIII) or DRV/r (BII) plus ABC/3TC if HLA-B*5701 negative
- DRV/c plus either TDF/FTC (BII) or TAF/FTC (BII)
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 (CII) plus ABC/3TC
- EFV plus ABC/3TC (CI)
- RAL plus ABC/3TC (CII)

Other Regimens to Consider when TAF, TDF, or ABC Cannot be Used:

- DRV/r plus RAL (BID) (CI)
- LPV/r plus 3TC (BID) (CI)

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

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 for 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-
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/mm3). 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](https://aidsinfo.nih.gov/guidelines) (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](https://aidsinfo.nih.gov/guidelines))

### 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.

<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count &lt;200 cells/mm³</td>
<td>Do Not Use the Following Regimens:</td>
<td>Higher rate of virologic failure observed in those with low pretreatment CD4 cell count.</td>
<td></td>
</tr>
<tr>
<td>HIV RNA &gt;100,000 copies/mL</td>
<td>Do Not Use the Following Regimens:</td>
<td>Higher rates of virologic failure observed in those with high pretreatment HIV RNA.</td>
<td></td>
</tr>
<tr>
<td>HLA-B*5701 positive</td>
<td>Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Must treat before HIV drug resistance results available</td>
<td>Avoid NNRTI-based regimens.</td>
<td>Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommended ART Regimens:</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/r plus TAF/FTC or TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DTG plus TAF/FTC or TDF/FTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 2 of 4)

<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
</table>
| 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/mm³  
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/mm³, 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. |
|                                   | 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. |
### Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 3 of 4)

<table>
<thead>
<tr>
<th>Presence of Other Conditions, continued</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>Psychiatric illnesses</td>
<td>Consider avoiding EFV- and RPV-based regimens.</td>
<td>EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality.</td>
</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>HIV-associated dementia (HAD)</td>
<td>Avoid EFV-based regimens if possible. Favor DRV-based or DTG-based regimens.</td>
<td>EFV-related neuropsychiatric effects may confound assessment of ART’s beneficial effects on improvement of HAD-related symptoms. Theoretical CNS penetration advantage</td>
</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>Narcotic replacement therapy required</td>
<td>If patient is receiving methadone, consider avoiding EFV-based regimens. If EFV is used, an increase in methadone dose may be necessary.</td>
<td>EFV reduces methadone concentrations and may lead to withdrawal symptoms.</td>
</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>High cardiac risk</td>
<td>Consider avoiding ABC- and LPV/r-based regimens.</td>
<td>Increased cardiovascular risk in some studies</td>
</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>Hyperlipidemia</td>
<td>The Following ARV Drugs have been Associated with Dyslipidemia: • PI/r or PI/c • EFV • EVG/c</td>
<td>DTG and RAL have fewer lipid effects. TDF has been associated with more favorable lipid effects than ABC or TAF.</td>
</tr>
<tr>
<td>Presence of Other Conditions, continued</td>
<td>Pregnancy</td>
<td>Refer to the Perinatal Guidelines.</td>
<td></td>
</tr>
<tr>
<td>Presence of Coinfections</td>
<td>HBV infection</td>
<td>Use TDF or TAF, with FTC or 3TC, whenever possible. If TDF and TAF are Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).</td>
<td>TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug active against HBV.</td>
</tr>
<tr>
<td>Presence of Coinfections</td>
<td>HCV treatment required</td>
<td>Refer to recommendations in HCV/HIV Coinfection.</td>
<td></td>
</tr>
<tr>
<td>Presence of Coinfections</td>
<td>Treating TB disease with rifamycins</td>
<td>TAF is not recommended with any rifamycin-containing regimen. • Rifamycins may significantly reduce TAF exposure.</td>
<td>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.</td>
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</tbody>
</table>

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

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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 same11-13 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 to 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
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.6 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 participants, 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
**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25-28} Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.\textsuperscript{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.
• 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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*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

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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.\(^\text{54,55}\) 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.\(^\text{56}\)

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 \(<60\ \text{mL/min})\),\(^\text{57}\) 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.
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
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.53
- 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).
**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. RAL was superior to EFV at 4 and 5 years 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.
  - 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.

**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.

**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).
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 and the drugs’ low genetic barrier for the development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients. 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. 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/mm³) 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.
- 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.
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.

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.
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks. RAL was superior to EFV at 4 and 5 years, 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.

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. Study drug-related adverse
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. This association, however, was not found in analyses of 3 large observational cohorts.

- 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. 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. 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
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/mm³ than in those with CD4 counts ≥200 cells/mm³.

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...
• Pretreatment viral load <100,000 copies/mL and CD4 count >200 cells/mm³.

• 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. 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. 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. This association was not seen with ATV. 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.

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

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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, and superior at week 192. 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.

- 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.

- A small retrospective study that followed participants for 48 weeks suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients.

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. 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 ($P \leq 0.02$).

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).
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 cholelithiasis95 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
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. 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.

**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.

**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
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/mm³, 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/µL and CD4 cell counts >200 cells/mm³, 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.
### 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.

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
</table>
| **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.  
• 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 |
| | 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 | • 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) |
| **INSTI** | DTG | • Once-daily dosing  
• Higher barrier to resistance than EVG or RAL  
• Coformulated with ABC and 3TC  
• No food requirement  
• No CYP3A4 interactions | |
| | 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) |
### Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy  (page 2 of 3)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
</table>
| 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) | |
| NNRTIs | 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/mm³ 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) |
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy  (page 3 of 3)

<table>
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<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>ATV/c</td>
<td>Coformulated tablet</td>
<td>• COBI inhibits active tubular secretion of Cr and can increase serum Cr.</td>
<td></td>
</tr>
<tr>
<td>(Specific considerations)</td>
<td></td>
<td>• Coadministration with TDF is not recommended in patients with CrCl &lt;70 mL/min</td>
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<tr>
<td></td>
<td></td>
<td>• Less long-term clinical experience than for ATV/r</td>
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<tr>
<td></td>
<td></td>
<td>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</td>
<td></td>
</tr>
<tr>
<td>DRV/c or DRV/r</td>
<td>Once-daily dosing</td>
<td>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL</td>
<td>• Skin rash</td>
</tr>
<tr>
<td>(DRV-specific considerations)</td>
<td></td>
<td>• PI resistance at the time of treatment failure uncommon with PK-enhanced PIs</td>
<td>• Food requirement</td>
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<td></td>
<td></td>
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<td>DRV/c</td>
<td>Coformulated tablet</td>
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<td></td>
<td>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.</td>
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<td></td>
<td>• Coadministration with TDF is not recommended in patients with CrCl &lt;70 mL/min</td>
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<tr>
<td></td>
<td></td>
<td>• 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</td>
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<tr>
<td></td>
<td></td>
<td>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>Only RTV-coformulated PI</td>
<td>• Requires 200 mg per day of RTV</td>
<td>• Possible higher risk of MI associated with cumulative use of LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No food requirement</td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Once or twice daily dosing</td>
<td>• Possible nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)</td>
</tr>
</tbody>
</table>

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; Ca = calcium; CaCO3 = 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

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents F-27

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

<table>
<thead>
<tr>
<th>ARV Drugs or Components</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
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<tr>
<td>ABC/3TC/ZDV (Co-Formulated) As triple-NRTI combination regimen</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>ABC/3TC/ZDV plus TDF As quadruple-NRTI combination regimen</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>d4T plus 3TC</td>
<td>• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis</td>
</tr>
</tbody>
</table>
| 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 |
Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

<table>
<thead>
<tr>
<th>ARV Drugs or Components</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFV</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td>RTV as sole PI</td>
<td>• High pill burden</td>
</tr>
<tr>
<td></td>
<td>• GI intolerance</td>
</tr>
<tr>
<td></td>
<td>• Metabolic toxicity</td>
</tr>
<tr>
<td>SQV (Unboosted)</td>
<td>• Inadequate bioavailability</td>
</tr>
<tr>
<td></td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>SQV/r</td>
<td>• High pill burden</td>
</tr>
<tr>
<td></td>
<td>• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG</td>
</tr>
<tr>
<td>TPV/r</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Higher rate of adverse events than other RTV-boosted PIs</td>
</tr>
<tr>
<td></td>
<td>• Higher dose of RTV required for boosting than other RTV-boosted PIs</td>
</tr>
<tr>
<td>CCR5 Anagonist</td>
<td></td>
</tr>
<tr>
<td>MVC</td>
<td>• Requires testing for CCR5 tropism before initiation of therapy</td>
</tr>
<tr>
<td></td>
<td>• No virologic benefit when compared with other recommended regimens</td>
</tr>
<tr>
<td></td>
<td>• Requires twice-daily dosing</td>
</tr>
</tbody>
</table>

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI= cobicistat; d4T = stavudine; ddl = 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; IDV = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; 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
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents


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