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

On November 18, 2015, the U.S. Department of Health and Human Services’ Panel on Antiretroviral Guidelines for Adults and Adolescents issued a statement regarding the inclusion of elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine as a Recommended regimen for patients with pre-antiretroviral therapy CrCl ≥30 mL/min. An updated What to Start section with discussion regarding this regimen will be available in the next update of the Guidelines.

Panel’s Recommendations

- An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir).
- The Panel classifies the following regimens as Recommended regimens for antiretroviral-naive patients:
  - **Integrase Strand Transfer Inhibitor-Based Regimens:**
    - Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI)
    - Dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (AI)
  - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine—only for patients with pre-antiretroviral therapy CrCl ≥30 mL/min
  - Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine—only for patients with pre-antiretroviral therapy CrCl >70 mL/min (AI)
  - Raltegravir plus tenofovir/emtricitabine (AI)
  - **Protease Inhibitor-Based Regimen:**
    - Darunavir/ritonavir plus tenofovir disoproxil fumarate/emtricitabine (AI)
  - On the basis of individual patient characteristics and needs, an Alternative regimen or, less frequently, an Other regimen may in some instances be the optimal regimen for a patient. A list of Alternative and Other regimens can be found in Table 6.
  - Given the large number of excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, and cost. Table 7 provides guidance on choosing an antiretroviral regimen based on selected clinical case scenarios. Table 8 highlights the advantages and disadvantages of different components in a regimen.

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

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

Lamivudine may substitute for emtricitabine or vice versa.

Introduction

More than 25 antiretroviral (ARV) drugs in 6 mechanistic classes are Food and Drug Administration (FDA) approved for treatment of HIV infection. These six 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 (pharmacokinetic [PK] enhancers or boosters) are used solely to improve the pharmacokinetic profiles of some ARV drugs (e.g., PIs and the INSTI elvitegravir [EVG]).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir plus lamivudine (ABC/3TC) or tenofovir disoproxil fumarate plus 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
Data Used for Making Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)’s recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In select cases, the Panel considers data presented in abstract format at major scientific meetings. The Panel’s first criterion for selection of evidence on which to base recommendations is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen has shown high rates of viral suppression, increased CD4 cell count, and has a favorable safety profile. Comparative clinical trials of initial treatments generally show no significant differences in HIV-related clinical endpoints or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events. When developing recommendations, the Panel also considers 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. Each of the regimens listed in Table 6 has shown potent virologic efficacy as measured by the proportion of participants in comparative clinical trials able to achieve and maintain viral suppression. Recommended regimens are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. 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 individual patient characteristics and needs, an Alternative regimen may actually be the optimal regimen for a specific patient. Some regimens are classified as Other regimens because, 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 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 list characteristics of individual ARV agents, such as formulations, dosing recommendations, PKs, and 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 these guidelines, new data from clinical trials and cohort studies, as well as experience in clinical practice, have prompted significant changes to the list of Recommended, Alternative, and Other regimens for treatment-naive patients (Table 6). Among these changes, the following deserve emphasis:

• There are now five Recommended regimens for antiretroviral therapy (ART)-naive patients: four INSTI-based regimens and one ritonavir-boosted PI (PI/r)-based regimen.

• Results from a large comparative clinical trial comparing atazanavir/ritonavir (ATV/r) plus TDF/FTC to darunavir/ritonavir (DRV/r) or raltegravir (RAL) plus TDF/FTC showed a greater rate of toxicities-related discontinuation in the ATV/r arm. Therefore, ATV/r plus TDF/FTC has been moved from the Recommended to the Alternative category.

• The Panel has also moved EFV/TDF/FTC from the Recommended to the Alternative category because of concerns about the tolerability of efavirenz (EFV) in clinical trials and practice, especially the high rate of central nervous system (CNS) related toxicities, and a possible association with suicidality observed in one analysis of four clinical trials.
Regimens that were previously listed as Recommended for patients with baseline HIV RNA <100,000 copies/mL or CD4 count >200 cells/mm³ are now in the Alternative or Other category, with the same caveat to limit their use to patients with the cited HIV RNA and CD4 levels.

Two regimens that use fewer than two NRTIs (DRV/r plus RAL and lopinavir/ritonavir [LPV/r] plus 3TC) are listed among the Other regimens, with the caveat that their use be limited to patients who cannot take either TDF or ABC.

Coformulations of ATV and DRV with the PK enhancer cobicistat (COBI) have been added to the Alternative regimen options.

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

An ARV regimen generally consists of two NRTIs (one of which is FTC or 3TC) plus an INSTI, NNRTI, or PK-enhanced PI. Selection of a regimen should be individualized on the basis of virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, a patient’s resistance test results and comorbid conditions, and cost. Table 7 lists specific case scenarios to guide regimen selection for patients with common clinical conditions. For more detailed recommendations on ARV choices and dosing in HIV-infected pregnant women, refer to the latest perinatal guidelines available at http://aidsinfo.nih.gov/guidelines.

Table: Recommended and Alternative Regimen Options

<table>
<thead>
<tr>
<th>Recommended Regimen Options</th>
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</thead>
<tbody>
<tr>
<td><strong>INSTI-Based Regimens:</strong></td>
</tr>
<tr>
<td>• DTG/ABC/3TC&lt;sup&gt;a&lt;/sup&gt; — only for patients who are HLA-B*5701 negative (AI)</td>
</tr>
<tr>
<td>• DTG plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td>• EVG/c/TAF/FTC&lt;sup&gt;a&lt;/sup&gt; — only for patients with pre-treatment estimated CrCl ≥30 mL/min (AI)</td>
</tr>
<tr>
<td>• EVG/c/TDF/FTC&lt;sup&gt;a&lt;/sup&gt; — only for patients with pre-treatment estimated CrCl ≥70 mL/min (AI)</td>
</tr>
<tr>
<td>• RAL plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; (AI)</td>
</tr>
<tr>
<td><strong>PI-Based Regimens:</strong></td>
</tr>
<tr>
<td>• DRV/r plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; (AI)</td>
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<table>
<thead>
<tr>
<th>Alternative Regimen Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI-Based Regimens:</strong></td>
</tr>
<tr>
<td>• EFV/TDF/FTC&lt;sup&gt;a&lt;/sup&gt; (BI)</td>
</tr>
<tr>
<td>• RPV/TDF/FTC&lt;sup&gt;a&lt;/sup&gt; — only for patients with pre-treatment HIV RNA &lt;100,000 copies/mL and CD4 cell count &gt;200 cells/mm³ (BI)</td>
</tr>
<tr>
<td><strong>PI-Based Regimens:</strong></td>
</tr>
<tr>
<td>• ATV/c plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; — only for patients with pre-treatment estimated CrCl ≥70 mL/min (BI)</td>
</tr>
<tr>
<td>• ATV/r plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; (BI)</td>
</tr>
<tr>
<td>• (DRV/c or DRV/r) plus ABC/3TC&lt;sup&gt;a&lt;/sup&gt; — only for patients who are HLA-B*5701 negative (BII for DRV/c and BII for DRV/r)</td>
</tr>
<tr>
<td>• DRV/c plus TDF/FTC&lt;sup&gt;a&lt;/sup&gt; — only for patients with pre-treatment estimated CrCl ≥70 mL/min (BII)</td>
</tr>
</tbody>
</table>
Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients  (page 2 of 2)

<table>
<thead>
<tr>
<th>Other Regimen Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Drugs classes and regimens within each class are arranged in alphabetical order.)</td>
</tr>
</tbody>
</table>

Regimens that, in comparison with Recommended and Alternative 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.

**INSTI-Based Regimen**

- **RAL plus ABC/3TC**—only for patients who are HLA-B*5701 negative (CII)

**NNRTI-Based Regimen**

- **EFV plus ABC/3TC**—only for patients who are HLA-B*5701 negative and with pre-treatment HIV RNA <100,000 copies/mL (CI)

**PI-Based Regimens**

- **(ATV/c or ATV/r) plus ABC/3TC**—only for patients who are HLA-B*5701 negative and with pre-treatment HIV RNA <100,000 copies/mL (CIII for ATV/c and CI for ATV/r)
- **LPV/r** (once or twice daily) plus ABC/3TC—only for patients who are HLA-B*5701 negative (CI)
- **LPV/r** (once or twice daily) plus TDF/FTC (CI)

**Other Regimens When TDF or ABC Cannot be Used**

- **DRV/r plus RAL**—only for patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm³ (CI)
- **LPV/r** (twice daily) plus 3TC (twice daily) (CI)

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

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

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### Considerations When Selecting a Regimen for Antiretroviral Therapy-Naive Patients

As noted in Table 6, the Recommended Regimens include four INSTI-based regimens and one DRV/r-based regimen for initial therapy. The INSTI-based regimens were selected because of their high virologic efficacy, excellent safety and tolerability profiles, and (with RAL and dolutegravir [DTG]) low number of drug-drug interactions (see the INSTI section for discussion regarding the special characteristics and clinical trial results for each of the 3 Recommended INSTIs). For patients who are at high risk for intermittent therapy because of poor adherence or have transmitted NRTI drug resistance, a PI/r-based treatment is preferred given the PIs high genetic barrier to resistance (see PI section for discussion of the different PK-boosted PIs recommended by the Panel). In some situations, an NNRTI-based regimen may be a better choice for a particular patient. **Table 7** provides guidance on regimen selection based on various patient- and regimen-specific characteristics.

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*Note*: The following are available as co-formulated fixed-dose combination products: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TDF/FTC, and TDF/FTC.

**Key to Acronyms**: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/c = cobicistat-boosted atazanavir; ATV/r = ritonavir-boosted atazanavir; CrCl = creatinine clearance; DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c/TAF/TFC = elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir DF/emtricitabine; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
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, with the goal of providing 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 of the Patient:
- Pre-treatment HIV RNA level (viral load)
- Pre-treatment CD4 cell count
- HIV genotypic drug resistance testing results
- HLA-B*5701 status
- Patient preferences
- Patient’s anticipated adherence

Specific Comorbidities or Other Conditions:
- Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, neurologic disease, drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or pregnancy potential. Clinicians should refer to the latest Perinatal Guidelines for more detailed recommendations on the safety and effectiveness of ARV drugs during pregnancy.
- Coinfections: hepatitis C (HCV), hepatitis B (HBV), tuberculosis (TB)

Regimen-Specific Considerations:
- Regimen’s genetic barrier to resistance
- Potential adverse drug effects
- Known or potential drug interactions with other medications
- Convenience (e.g., pill burden, dosing frequency, availability of fixed-dose combination products, food requirements)
- Cost (see Cost Consideration and Antiretroviral Therapy section)
Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 1 of 3)

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>Pre-ART Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 pre-treatment 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 pre-treatment HIV RNA</td>
<td></td>
</tr>
<tr>
<td>HLA-B*5701 positive</td>
<td>Do not use ABC-containing regimen.</td>
<td>Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.</td>
<td></td>
</tr>
<tr>
<td>Must treat before HIV drug resistance results available</td>
<td>Avoid NNRTI-based regimen.</td>
<td>Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. Some experts avoid using INSTI-containing regimens in this setting because of concern regarding their ability to fully suppress viral replication if transmitted NRTI mutations are present.</td>
<td></td>
</tr>
<tr>
<td>ART Specific Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One pill once daily regimen desired</td>
<td>ART Options Include:</td>
<td>Available as fixed-dose combination tablets</td>
<td></td>
</tr>
<tr>
<td>Food effects</td>
<td>Regimens that Should be Taken with Food:</td>
<td>Food improves absorption of the listed regimens. Taking EFV-based regimens with food increases EFV absorption and may increase CNS side effects.</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 2 of 3)

<table>
<thead>
<tr>
<th>Presence of Other Conditions</th>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of Other Conditions</td>
<td>Chronic kidney disease (defined as eGFR &lt;60 mL/min)</td>
<td>Consider avoiding TDF.</td>
<td>If eGFR is &lt;70 mL/min, Do Not Use: EVG/c/TDF/FTC, or ATV/c with TDF, or DRV/c with TDF. Options for CKD Patients Use ABC/3TC if HLA-B*5701 Negative: If HIV RNA &gt;100,000 copies/mL, do not use ABC/3TC with EFV or ATV/r. If CrCl &lt;50 mL/min, do not use coformulated ABC/3TC because 3TC requires dose adjustment. <strong>Other Options (See Text for Discussion):</strong> DRV/r plus RAL (if HIV &lt;100,000/mL and CD4 count &gt;200/mm³), or LPV/r plus 3TC, or Modify TDF dose.</td>
<td>TDF has been associated with renal tubulopathy. See Appendix B, Table 7 for recommendations on ARV dose modification.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Osteoporosis</td>
<td>Consider avoiding TDF.</td>
<td>Use ABC/3TC if HLA-B*5701 negative If HIV RNA &gt;100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r)</td>
<td>TDF is associated with greater decrease in bone mineral density along with renal tubulopathy, urine phosphate wasting, and osteomalacia.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Psychiatric illnesses</td>
<td>Consider avoiding EFV-based regimens.</td>
<td></td>
<td>EFV can exacerbate psychiatric symptoms and may be associated with suicidality.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>HIV-associated dementia (HAD)</td>
<td>Avoid EFV-based regimens if possible. Favor DRV-based or DTG-based regimen.</td>
<td></td>
<td>EFV neuropsychiatric effects may confound assessment of the effect of ART on improvement of symptoms associated with HAD. Theoretical CNS penetration advantage</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Narcotic replacement therapy required</td>
<td>If patient receiving methadone, consider avoiding EFV-based regimen. If EFV is used, an increase in methadone dose may be necessary.</td>
<td></td>
<td>EFV reduces methadone concentrations and may lead to withdrawal symptoms.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>High cardiac risk</td>
<td>Consider avoiding ABC- and LPV/r - based regimens.</td>
<td></td>
<td>Increased cardiovascular risk in some studies (see ABC discussion in this section)</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Hyperlipidemia</td>
<td>The Following ARV Drug Classes or Drugs have been Associated with Deleterious Effects on Lipids: PI/r ABC EFV EVG/c</td>
<td></td>
<td>TDF has been associated with beneficial lipid effects, thus it may be preferable to ABC.</td>
</tr>
<tr>
<td>Presence of Other Conditions</td>
<td>Pregnancy</td>
<td>Refer to the Perinatal Antiretroviral Treatment Guidelines.</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Presence of Co-Infections</th>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV infection</td>
<td>Use TDF/FTC (or TDF plus 3TC) whenever possible. If TDF is Contraindicated: • For treatment of HBV, use FTC or 3TC with entecavir or another drug active against HBV. TDF, 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 HBV-active agent.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV treatment required</td>
<td>Refer to recommendations in the HIV/HCV co-infection section.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB infection</td>
<td>If Rifampin is Used: • EFV-based regimens have the least drug-drug interactions. • If RAL is used, increase RAL dose to 800mg BID. • Use DTG at 50mg BID dose only in patients without selected INSTI mutations (refer to product label). If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen. 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.</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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<td></td>
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</tbody>
</table>

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

Selecting an Initial Antiretroviral Regimen

Initial therapy generally consists of two NRTIs combined with an INSTI, an NNRTI, or a pharmacologically boosted PI. All Recommended and Alternative regimens include the NRTI combination of TDF/FTC or ABC/3TC. Both TDF/FTC and ABC/3TC are available as fixed-dose combination tablets. The choice of NRTI combination is usually guided by differences between TDF and ABC given that FTC and 3TC have comparable efficacy and limited potential for adverse events. Considerations when deciding between TDF and ABC are summarized in Table 8 and in the section on Dual NRTI options (below).

Choosing Between an Integrase Strand Transfer Inhibitor-, a Non-Nucleoside Reverse Transcriptase Inhibitor-, or a Protease Inhibitor-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; and concomitant medications and the potential for drug-drug interactions (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

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effects, and (with RAL and DTG) have no significant CYP 3A4-associated drug interactions. In addition, in the two head-to-head comparisons between DRV/r- and INSTI-containing regimens, the INSTI was better tolerated, with fewer treatment discontinuations.\(^4\,6\) 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. In this context, DRV/r may have an important role given its high genetic barrier to resistance and low rate of treatment-emergent resistance during many years of clinical experience.

Alternative Regimens include either an NNRTI-based (EFV or rilpivirine [RPV]) or a PK-enhanced, PI-based (ATV/r, atazanavir/cobicistat [ATV/c], or darunavir/cobicistat [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 CNS-related side effects associated with the EFV-based regimens makes them less tolerable than other regimens. RPV has fewer adverse effects than EFV, is available as the smallest coformulated single tablet, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA (>100,000 copies/mL) and low CD4 count (<200 cells/mm\(^3\)). ATV/r has demonstrated excellent virologic efficacy in clinical trials, and has fewer metabolic adverse effects than other boosted PI regimens; however, recent clinical trial data showed that ATV/r had a higher rate of adverse effect-associated drug discontinuation than the comparators (DRV/r and RAL). Thus, despite these favorable attributes, based on the above considerations, EFV-, RPV-, and ATV/r-containing regimens are no longer Recommended Regimens as initial therapy in all patients, and are listed as Alternatives. 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.

**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, including information related to the safety and virologic efficacy of different drugs based on clinical trial results and/or post-marketing data, special considerations to take into account, and the rationales for the Panel’s recommendations.

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

**Summary**

TDF/FTC and ABC/3TC are NRTI combinations commonly used for 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 Abacavir/Lamivudine to Tenofovir/Emtricitabine**

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each with the same\(^7\,9\) or a different third ARV drug (also see discussion in the DTG section).\(^10\)

- 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 \(\geq 100,000\) copies/mL. HLA B*5701 testing was not required before study entry.
- A Data Safety Monitoring Board recommended early termination of the \(\geq 100,000\) 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.\(^7\) 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 between ABC/3TC and TDF/FTC in time to virologic failure for participants who had plasma HIV RNA <100,000 copies/mL at screening.\(^11\)
- The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA B*5701-negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. At week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants than among TDF/FTC-treated participants.\(^8\)
- 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 \(\geq\) 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.\(^9\)

**Dual-Nucleoside Reverse Transcriptase Inhibitor Choices**

**Note:** In alphabetical order.

**Abacavir/Lamivudine**

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.\(^10,12-14\)

**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.\(^15,16\) 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 re-challenged, 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 (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.\(^17,18\)
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association;\(^19-22\) others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.\(^23-27\)
- 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 co-formulated 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 is an alternative to TDF in patients with underlying renal dysfunction or who are at risk for renal effects. No dosage adjustment is required in patients with renal dysfunction.
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 co-formulated products, the Panel classifies ABC/3TC plus DTG as a Recommended regimen (AI) (see discussion regarding DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, or ATV/c is only recommended for patients with pre-treatment HIV RNA <100,000 copies/mL.
- ABC/3TC is a part of several Alternative or Other regimens when combined with another ARV drug. See Table 6 for more detailed recommendations on use of ABC/3TC with other drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

Tenofovir/Emtricitabine

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.68-37

Adverse Effects:

- New onset or worsening renal impairment has been associated with TDF use.38,39 Risk factors may include advanced HIV disease; longer treatment history; low body weight, especially in females;40 and pre-existing renal impairment.41
  - 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.39,42-46
- While initiation of all NRTI-containing regimens has been associated with a decrease in bone mineral density (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 bone mineral density than ABC/3TC-treated participants.47,48 Following an early decline after ART initiation, BMD generally stabilizes.
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.49

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, given once daily.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Monitoring section). In patients who have pre-existing renal insufficiency (CrCl <60 mL/min),50 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 should be used as the NRTI pair of the ART regimen because the drugs have activity against both viruses (also see HIV/HBV Coinfection section).

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 co-formulated products, the Panel considers TDF/FTC as a

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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.

**Integrase Strand Transfer Inhibitor-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 TDF/FTC. EVG is also available as a single agent designed to be used in combination with PI/r in ART-experienced patients, and is not recommended for use in treatment-naive patients.

**Recommended Integrase Strand Transfer Inhibitor-Based Regimens**

**Note:** In alphabetical order.

**Dolutegravir**

**Efficacy in Clinical Trials:**

The efficacy of DTG in treatment-naive patients has been evaluated in three 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 non-inferior 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 in combination with investigator-selected NRTI ABC/3TC or TDF/FTC, in 822 participants. At week 96, DTG was non-inferior to RAL.37
- 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.10 At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.51
- 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.6,52 The difference in response rates favoring DTG was greater in patients with pre-treatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.53

**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 hypersensitivity reactions were reported in <1% of trial participants.

**Other Factors and Considerations:**

- In treatment-naive patients, DTG is given once daily, with or without food.
- 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 two-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 Interaction section). 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.

Panel’s Recommendation:

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

Elvitegravir

Elvitegravir is available as a component of a four-drug, fixed-dose combination product containing EVG, COBI, TDF, and FTC (EVG/c/TDF/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 non-inferior to fixed-dose EFV/TDF/FTC.54
• EVG/c/TDF/FTC was also found to be non-inferior to a combination containing ATV/r plus TDF/FTC.55

Adverse Effects:

• The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.54,55

Other Factors and Considerations:

• EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.

• Because COBI inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see Drug-Drug Interactions section).56

• EVG plasma concentrations are lower when the ARV is administered simultaneously with polyvalent cation-containing antacids or supplements (see Drug Interaction section). Separate EVG/c/TDF/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.57 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.56

• EVG/c/TDF/FTC is not recommended for patients with pre-treatment estimated CrCl <70 mL/min.46

• At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.54,55 These mutations conferred cross-resistance to RAL, with most retaining susceptibility to DTG.
Panel’s Recommendation:

- On the basis of the above factors, the Panel classifies EVG/c/TDF/FTC as a Recommended regimen in ART-naive patients (AI).

Raltegravir

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 non-inferior to EFV at 48 weeks.33 RAL was superior to EFV at 4 and 5 years,36,58 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 non-inferior 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 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.37
- 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. Lipids increased more in participants in the 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.4

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.59

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. Raltegravir 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.

Panel’s Recommendations:

- On the basis of these data and long-term clinical experience with RAL, the Panel considers RAL plus TDF/FTC as a Recommended regimen in ARV-naive patients (AI).
• 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 therapy (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 (see Drug-Resistance Testing). High-level resistance to all NNRTIs (except ETR) may occur with a single mutation; within-class cross-resistance is common. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross resistance to other NNRTIs, including ETR.

Efavirenz

EFV is an NNRTI approved for use in combination with 2-NRTIs for ART-naive patients.

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 non-inferiority to several comparator regimens.

• In ACTG 5142, EFV was superior to LPV/r, although drug resistance was more common after EFV failure than after LPV/r failure.
• In the 2NN study, compared to EFV, NVP did not meet non-inferiority criteria.
• 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 non-inferior to RPV, with less virologic failure but 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 non-inferior to EVG/c/TDF/FTC.

More recently, 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 non-inferior 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.

A recent multinational randomized placebo-controlled trial compared two once daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg (reduced dose). At 48 weeks,
EFV 400 mg was non-inferior 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 two 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 co-formulated as a component of a single pill regimen.

**Adverse Effects:**
- EFV can cause CNS side effects, such as abnormal dreams, dizziness, headache, and depression, which resolve over a period of days to weeks in most patients. However, more subtle, long-term neuropsychiatric effects can occur. A recent analysis of 4 AIDS Clinical Trial Group (ACTG) comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens. This association, however, was not found in analyses of two 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.
- EFV has been associated with CNS birth defects in non-human 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).

**Panel's Recommendations:**
- Given the availability of regimens with fewer treatment-limiting adverse events with non-inferior or superior efficacy, the Panel classifies EFV/TDF/FTC as an Alternative regimen for ART-naive patients (BI).
- 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 until further data to support its use in the U.S. population are available.

**Rilpivirine**
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 non-inferior 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 $<$200 cells/mm$^3$ than in those with CD4 counts $\geq$ 200 cells/mm$^3$.

STaR, a Phase 3b, open-label study, compared the fixed-dose combinations of RPV/TDF/FTC and EFV/TDF/FTC in 786 treatment-naive patients. At 96 weeks, the following key findings were reported:\(^67\)

- RPV was non-inferior to EFV overall.
- RPV was superior to EFV in patients with pre-ART viral loads $\leq$ 100,000 copies/mL and non-inferior 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.
- At 48 weeks, NRTI and NNRTI resistance occurred in 2% and 1% of RPV- and EFV-treated patients, respectively, with viral loads $\leq$ 100,000; in 5% and 0% of RPV- and EFV-treated patients, respectively, with viral loads 100,000 to 500,000; and in 19% and 4% of RPV- and EFV-treated patients, respectively, with viral loads $>$500,000 copies/mL.

**Adverse Effects:**

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer CNS adverse events (e.g., 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.

**Other Factors and Considerations:**

- RPV is formulated both as a single-drug tablet and in a fixed-dose combination tablet with TDF/FTC. Among available single pill regimens, it is the smallest tablet.
- RPV/TDF/FTC is given as a once daily regimen, and must be administered with a meal (at least 400 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 Interaction section for dosing recommendations).
- RPV is primarily metabolized in the liver by CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug Interaction section).
- 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.

**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 as an Alternative regimen.
- Use of RPV with TDF/FTC should be limited to ART-naive patients with pre-treatment viral load $<$100,000 copies/mL and CD4 count $>$200 cells/mm$^3$ (BI).
- Data on RPV with ABC/3TC are insufficient to consider recommending this regimen as a Recommended, Alternative, or Other regimen.

**Protease Inhibitor-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 (particularly...
with PK enhancement) have demonstrated virologic potency and (for those with RTV boosting) 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.\textsuperscript{72,73} 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 section). 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.

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 pharmacokinetic 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.\textsuperscript{18,24} This association was not seen with ATV.\textsuperscript{74} Because of the limited number of patients receiving DRV/r, this boosted-PI was not included in the analysis of the two studies.

Recommended PIs 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. 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.\textsuperscript{4} Because of its higher rate of adverse effects, the Panel now classifies ATV/r plus TDF/FTC as an Alternative regimen (BI). ATV/c- and DRV/c-based regimens are considered Alternative PI regimens for the reasons detailed below.

LPV/r has twice the daily dose of RTV as other PI/r and is associated with more metabolic complications and gastrointestinal side effects than PK-enhanced ATV or DRV. LPV/r remains as an Other PI/r because it is currently the only PI co-formulated with RTV and it has extended experience in clinical trials and practice. 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 no longer included as an option for initial therapy. Nonetheless, patients who are doing well on regimens containing these PIs should not necessarily be switched to other agents.

**Recommended Protease Inhibitor-Based Regimen**

**Darunavir/Ritonavir**

**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, non-inferiority trial. DRV/r was non-inferior to LPV/r at week 48,\textsuperscript{31} and superior at week 192.\textsuperscript{75} 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 two NRTIs, in 488 ART-naive participants. The rate of virologic suppression at week 48 was significantly greater among those who received DTG than in those who received DRV/r, largely because of more drug discontinuations in the DRV/r group.\textsuperscript{6}
- A small retrospective study that followed participants for 48 weeks suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients.\textsuperscript{76}
- The ACTG A5257 study 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.\textsuperscript{4}
Adverse Effects:

- In the ARTEMIS Study, grades 2 to 4 adverse events, primarily diarrhea, were seen less frequently in DRV/r recipients than in LPV/r recipients.
- 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.

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 section).

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 as a Recommended regimen (AI). 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 or Atazanavir/Cobicistat

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, non-inferiority study, the 2 regimens showed similar virologic and CD4 responses at 48 weeks and at 96 weeks.  
- 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. In a separate analysis, women assigned to ATV/r were found to have a higher risk of virologic failure than women assigned to EFV or men assigned to ATV/r.  
- 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.  
- ACTG A5257, a large randomized open-label trial, compared ATV/r with DRV/r or RAL, each given with TDF/FTC. At week 96, all 3 regimens had similar virologic efficacy. However, 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. Bone mineral density decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.  
- The Gilead Study 114 enrolled 692 treatment-naive patients. 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. At 48 weeks, similar percentages of patients achieved virologic suppression, had adverse events, and changes in serum creatinine and indirect bilirubin levels.

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.
• Nephrolithiasis,80-82 nephrotoxicity,83 and cholelithiasis84 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 (e.g., antacids, H2 antagonists, and particularly PPIs) may impair absorption of ATV. Table 19a provides recommendations for use of ATV/c or ATV/r with these agents.
• ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications metabolized through this same pathway (see Drug Interaction section).
• ATV/c coadministered with TDF/FTC is not recommended for patients with CrCl <70 mL/min.

Panel’s Recommendations:
• On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TDF/FTC as Alternative regimens for ART-naive patients regardless of pre-treatment HIV RNA (BII).
• Because of an inferior virologic response seen in patients with a high baseline viral load, the Panel recommends ATV/r or ATV/c plus ABC/3TC as Other regimens. Use of the regimens should be limited to patients with pre-ART HIV RNA <100,000 copies/mL (CI).
• As noted earlier, ATV/c plus TDF/FTC is not recommended for patients with CrCl <70 mL/min.

Darunavir/Cobicistat
A combination of (DRV 800 mg with COBI 150 mg) is bioequivalent to (DRV 800 mg with RTV 100 mg) in healthy volunteers.85

Efficacy in Clinical Trial:
• In a single arm trial of treatment-naive (94%) and treatment-experienced (6%) patients, the co-formulated 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.86

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 co-formulated tablet.
• Coadministration with TDF is not recommended in patients with CrCl <70 mL/min.

Panel’s Recommendation:
• On the basis of the bioequivalence study and the single arm trial, the Panel recommends DRV/c plus TDF/FTC (BII) and DRV/c plus ABC/3TC (BIII) as Alternative Regimens for ART-naive patients.
• As noted earlier, DRV/c plus TDF/FTC is not recommended for patients with CrCl <70 mL/min.
Other Protease Inhibitor-Based Regimens

Lopinavir/Ritonavir

Efficacy in Clinical Trials:

- A 7-year follow-up study of LPV/r and 2 NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen.\(^8\)\(^7\)
- Results of clinical trials that compared LPV/r with ATV/r and DRV/r are discussed above, demonstrating more favorable safety and tolerability of ATV/r and DRV/r.
- In the ACTG 5142 study, at 96 weeks, a smaller proportion of patients who received LPV/r plus 2 NRTIs achieved viral suppression (HIV RNA <50 copies/mL) than those who received EFV plus 2 NRTIs. However, the CD4 cell response was greater with LPV/r, and there was less drug resistance associated with virologic failure.\(^6\)\(^3\)
- In the GARDEL study, patients were randomized to 3TC or a 2 NRTI combination, with all study participants receiving LPV/r. The results demonstrated non-inferiority of the two strategies.\(^8\)\(^8\)

Adverse Effects:

- In addition to diarrhea, major adverse effects of LPV/r include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these require pharmacologic management in some patients.
- In the D:A:D and French observational cohorts, cumulative use of LPV/r was associated with a slightly increased risk of MI.\(^1\)\(^8\),\(^2\)\(^4\)
- In another D:A:D study, LPV/r use was also reported as an independent predictor of chronic renal impairment.\(^8\)\(^3\)

Other Factors and Considerations:

- LPV/r must be boosted with 200 mg/day of RTV and is associated with higher rates of GI side effects and hyperlipidemia than ATV/r and DRV/r, both of which are boosted with 100 mg/day of RTV.
- LPV/r can be given once or twice daily.
- Once-daily dosing should not be used in pregnant women, especially during the third trimester, when LPV levels are expected to decline (see Perinatal Guidelines).
- LPV/r is currently the only available PI co-formulated with RTV.

Panel’s Recommendation:

- On the basis of greater potential for adverse events and higher RTV dose and pill burden than ATV/r and DRV/r, the Panel recommends LPV/r plus TDF/FTC or LPV/r plus ABC/3TC as Other regimens (CI).

Other Antiretroviral Regimens for Initial Therapy When Abacavir or Tenofovir 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 both TDF and ABC, such as in the case of a patient with pre-existing renal disease who is HLA B*5701 positive or at high risk of cardiovascular disease.

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 or TDF cannot be used.
**Darunavir/Ritonavir plus Raltegravir**

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 non-inferior 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/mm³, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pre-treatment HIV RNA ≥100,000 copies/mL. High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.

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

**Lopinavir/Ritonavir plus Lamivudine**

In the GARDEL study, 426 ART-naive patients were randomized to receive twice-daily LPV/r plus either open-label 3TC (twice daily) or two NRTIs selected by the study investigators. At 48 weeks, a similar number of patients in each arm had HIV RNA <50 copies/mL, meeting the study’s non-inferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus 2 NRTI regimen.

An important limitation of the GARDEL study is the use of LPV/r, twice daily dosing, and 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 as compared to pharmacokinetically 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 either TDF or ABC (CI).

In summary, the aggregate results from these two fully powered studies with NRTI-limiting regimens demonstrate that these initial strategies have significant deficiencies as compared to standard-of-care treatment approaches, in particular, disadvantages 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 when both TDF and ABC are contraindicated. Other less well-tested NRTI-limiting combinations are not recommended.
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>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Dual-NRTI | ABC/3TC      | • Co-formulated with DTG as an STR | • Inferior virologic responses in patients with baseline HIV RNA ≥100,000 copies/mL when given with EFV or ATV/r as compared with TDF/FTC in ACTG 5202 study. This difference was not seen when ABC/3TC was used in combination with DTG.  
• May cause life-threatening hypersensitivity reaction in patients positive for the HLA B*5701 allele. As a result, HLA-B*5701 testing required before use  
• ABC use has been associated with cardiac events in some but not all observational studies. |
|           | TDF/FTC      | • Co-formulated with EFV, EVG/c, and RPV as a STR  
• Active against HBV; recommended dual-NRTI for HIV/HBV co-infected 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 | • Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency  
• Decreases BMD more than other NRTI combinations |
| INSTI     | DTG          | • Once-daily dosing  
• May have higher barrier to resistance than EVG or RAL  
• Co-formulated with ABC and 3TC as an STR  
• No food requirement  
• No CYP3A4 interactions | • Oral absorption can be reduced by simultaneous administration with products containing polyvalent cations (e.g., Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.  
• Inhibits renal tubular secretion of Cr and can increase serum Cr, without affecting glomerular function  
• UGT substrate; potential for drug interactions (see Table 19d) |
|           | EVG/c        | • Co-formulated as a STR with TDF/FTC  
• Once daily dosing  
• Compared with ATV/r, causes smaller increases in total and LDL cholesterol | • EVGc/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; therapy 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 antacids containing polyvalent cations, such as Al, Ca, or Mg (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 |
|           | 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 significantly impaired by antacids containing Al or Mg; co-administration is not recommended (see dosing recommendations in Table 19d).  
• UGT substrate; potential for drug interactions (see Table 19d) |
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>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTIs</td>
<td>EFV</td>
<td>• Once-daily dosing</td>
<td>• Transmitted resistance more common than with PIs and INSTIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Co-formulated with TDF/FTC</td>
<td>• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long term clinical experience</td>
<td>• Teratogenic in non-human primates; avoid use in women who are trying to conceive or who are sexually active and not using contraception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EFV-based regimens (except for EFV plus ABC/3TC) have well documented efficacy in patients with high HIV RNA</td>
<td>• Dyslipidemia</td>
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<td></td>
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<td>• Greater risk of resistance at the time of treatment failure than with PIs</td>
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<td></td>
<td></td>
<td></td>
<td>• Skin rash</td>
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<td></td>
<td>• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Should be taken on an empty stomach (food increases drug absorption and CNS toxicities)</td>
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<tr>
<td></td>
<td>RPV</td>
<td>• Once-daily dosing</td>
<td>• Not recommended in patients with pre-ART HIV RNA &gt;100,000 copies/mL or CD4 count &lt;200 cells/mm3 because of higher rate of virologic failure in these patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Co-formulated with TDF/FTC</td>
<td>• Transmitted resistance more common than with PIs and INSTIs</td>
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<tr>
<td></td>
<td></td>
<td>• Smaller pill size than co-formulated DTG/ABC/3TC, EFV/TDF/FTC, and EVG/c/TDF/FTC</td>
<td>• More NNRTI-, TDF-, and 3TC-associated mutations at virological failure than with regimen containing EFV and two NRTIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Compared with EFV:</td>
<td>• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)</td>
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<tr>
<td></td>
<td></td>
<td>• Fewer discontinuations for CNS adverse effects</td>
<td>• Meal requirement (&gt;390 kcal)</td>
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<td></td>
<td></td>
<td>• Fewer lipid effects</td>
<td>• Requires acid for adequate absorption</td>
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<td></td>
<td></td>
<td>• Fewer rashes</td>
<td>• Contraindicated with PPIs</td>
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<td></td>
<td></td>
<td>• Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information).</td>
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<td></td>
<td></td>
<td></td>
<td>• Use with caution when coadministered with a drug known to increase the risk of torsades de pointes.</td>
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<tr>
<td>PIs</td>
<td>ATV/c or ATV/r</td>
<td>• Once-daily dosing</td>
<td>• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice</td>
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<td></td>
<td></td>
<td>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL</td>
<td>• Food requirement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PI resistance at the time of treatment failure uncommon with pharmacologically-boosted PIs</td>
<td>• Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ATV/c and ATV/r have similar virologic activity and toxicity profiles</td>
<td>• Nephrolithiasis, cholelithiasis, nephrotoxicity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• GI adverse effects</td>
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<td></td>
<td></td>
<td></td>
<td>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)</td>
</tr>
<tr>
<td></td>
<td>ATV/c-specific considerations</td>
<td>• Co-formulated tablet</td>
<td>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Coadministration with TDF is not recommended in patients with CrCl &lt;70 mL/min</td>
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<td></td>
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<td></td>
<td>• Less long term clinical experience than for ATV/r</td>
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<td></td>
<td></td>
<td></td>
<td>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</td>
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</table>
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 3)

<table>
<thead>
<tr>
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<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>PIs</td>
<td>DRV/c or DRV/r</td>
<td>• Once-daily dosing</td>
<td>• Skin rash</td>
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<tr>
<td></td>
<td></td>
<td>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL</td>
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<td>• PI resistance at the time of treatment failure uncommon with pharmacokinetically-boosted PIs</td>
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<td>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a)</td>
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<td></td>
<td>DRV/c-specific considerations</td>
<td>• Co-formulated tablet</td>
<td>• Less long-term clinical experience than for DRV/r</td>
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<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></td>
<td>• Co-administration with TDF is not recommended in patients with CrCl &lt;70 mL/min</td>
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<td></td>
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<td></td>
<td>• Approval primarily based on pharmacokinetic 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></td>
<td>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</td>
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<tr>
<td></td>
<td>LPV/r</td>
<td>• Only RTV-coformulated PI</td>
<td>• Requires 200 mg per day of RTV</td>
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<tr>
<td></td>
<td></td>
<td>• No food requirement</td>
<td>• Once-daily dosing not recommended in pregnant women</td>
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<td></td>
<td></td>
<td>• Once or twice daily dosing</td>
<td>• Possible higher risk of MI associated with cumulative use of LPV/r</td>
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<td></td>
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<td>• PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect</td>
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<td>• Possible nephrotoxicity</td>
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<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; ART = antiretroviral therapy; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/c = cobicistat-boosted atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; Ca = calcium; CaCO₃ = calcium carbonate; CNS = central nervous system; COBI= cobicistat; Cr = creatinine; CrCl = creatinine clearance; CYP = cytochrome P; DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; 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; STR = single tablet regimen; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis
<table>
<thead>
<tr>
<th>ARV Drugs or Components</th>
<th>Reasons for Not Recommending as Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/ZDV (Co-Formulated)</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>As triple-NRTI combination regimen</td>
<td></td>
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<tr>
<td>ABC plus 3TC plus ZDV plus TDF</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td>As quadruple-NRTI combination regimen</td>
<td></td>
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<tr>
<td>d4T plus 3TC</td>
<td>• Significant toxicities including lipodystrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis</td>
</tr>
<tr>
<td>ddI plus 3TC (or FTC)</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Limited clinical trial experience in ART-naive patients</td>
</tr>
<tr>
<td></td>
<td>• ddI toxicities such as pancreatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>ddI plus TDF</td>
<td>• High rate of early virologic failure</td>
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<td>• Rapid selection of resistance mutations</td>
</tr>
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<td></td>
<td>• Potential for immunologic nonresponse/CD4 cell decline</td>
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<tr>
<td></td>
<td>• Increased ddI drug exposure and toxicities</td>
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<tr>
<td>ZDV/3TC</td>
<td>• ZDV/3TC is generally not recommended as initial therapy because greater toxicities (including bone marrow suppression; GI toxicities; and mitochondrial toxicities such as lipodystrophy, lactic acidosis, and hepatic steatosis; skeletal muscle myopathy; and cardiomyopathy) than Recommended NRTIs.</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>DLV</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Inconvenient (three times daily) dosing</td>
</tr>
<tr>
<td>ETR</td>
<td>• Insufficient data in ART-naive patients</td>
</tr>
<tr>
<td>NVP</td>
<td>• Associated with serious and potentially fatal toxicity (hepatic events, severe rash, including SJS and TEN)</td>
</tr>
<tr>
<td></td>
<td>• When compared to EFV, NVP did not meet non-inferiority criteria</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
</tr>
<tr>
<td>ATV (Unboosted)</td>
<td>• Less potent than boosted ATV</td>
</tr>
<tr>
<td>DRV (Unboosted)</td>
<td>• Use without RTV has not been studied</td>
</tr>
<tr>
<td>FPV (Unboosted) or FPV/r</td>
<td>• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV.</td>
</tr>
<tr>
<td></td>
<td>• Less clinical trial data for FPV/r than for other PI/r</td>
</tr>
<tr>
<td>IDV (Unboosted)</td>
<td>• Inconvenient dosing (three times daily with meal restrictions)</td>
</tr>
<tr>
<td></td>
<td>• Fluid requirement</td>
</tr>
<tr>
<td></td>
<td>• IDV toxicities such as nephrolithiasis, crystalluria</td>
</tr>
<tr>
<td>IDV/r</td>
<td>• Fluid requirement</td>
</tr>
<tr>
<td></td>
<td>• IDV toxicities such as nephrolithiasis, crystalluria</td>
</tr>
<tr>
<td>NFV</td>
<td>• Inferior virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
</tbody>
</table>
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>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 pre-treatment 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>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; d4T = stavudine; ddl = didanosine; DLV = delavirdine; DRV = darunavir; ETR = etravirine; FPV = fosamprenavir; FPV/r = ritonavir-boosted fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

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