



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

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 10/19/2018

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <https://aidsinfo.nih.gov/e-news>.

# What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated March 27, 2018; last reviewed March 27, 2018)

**NOTE:** The Panel has issued the following statement on bictegravir: <https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv>.

| Panel's Recommendations   |
|---|
| <ul style="list-style-type: none"><li>An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir).</li><li>The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as <b>Recommended Initial Regimens for Most People with HIV (in alphabetical order)</b>:<ul style="list-style-type: none"><li>Dolutegravir/abacavir/lamivudine<sup>a</sup>—<b>only</b> for patients who are HLA-B*5701-negative (<b>AI</b>)</li><li>Dolutegravir plus tenofovir/emtricitabine<sup>a,b</sup> (<b>AI</b>)</li><li>Elvitegravir/cobicistat/tenofovir/emtricitabine<sup>b</sup> (<b>AI</b>)</li><li>Raltegravir plus tenofovir/emtricitabine<sup>a,b</sup> (<b>AI</b> for tenofovir disoproxil fumarate, <b>AI</b> for tenofovir alafenamide)<sup>a,b</sup></li></ul></li><li>To address individual patient characteristics and needs, the Panel also provides a list of Recommended Initial Regimens in Certain Clinical Situations (Table 6).</li><li>Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 8 highlights the advantages and disadvantages of different components in a regimen.</li></ul> |
| <p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion</p>  |

<sup>a</sup> Lamivudine may substitute for emtricitabine or vice versa.

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

## Introduction

More than 25 antiretroviral (ARV) drugs in six 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, ritonavir (RTV or r) and cobicistat (COBI or c) are used solely as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of some ARV drugs (e.g., PIs and the INSTI elvitegravir [EVG]).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide (TAF)/emtricitabine (FTC) or tenofovir disoproxil fumarate (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 suppression of HIV replication and CD4 T lymphocyte (CD4) cell increases in most persons with HIV.<sup>1-3</sup>

## Supporting Evidence and Rationale Used for Panel's Recommendations

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

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

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

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

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

There are many other ARV regimens that are effective for initial therapy, but have disadvantages compared with the regimens listed in [Table 6](#). These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These other regimens are no longer included in [Table 6](#). A person with HIV who is virologically suppressed and who is not experiencing any adverse effects on a regimen that is not listed in [Table 6](#) need not necessarily change to a regimen that is in that table.

Regimens and medications listed in [Table 9](#) are not recommended. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in [Table 9](#) to a recommended regimen.

In addition to these tables, a number of tables presented below and at the end of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (Adult and Adolescent Guidelines) provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. [Table 8](#) lists the potential advantages and disadvantages of the different antiretroviral drug components. [Appendix B, Tables 1–6](#) lists characteristics of individual ARV agents (e.g., 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, there have been several important changes in the Panel's recommendations for initial therapy of people with HIV. Among these changes, the following deserve emphasis:

- INSTI-based regimens are recommended as initial therapy for most people with HIV. In large clinical trials and in clinical practice, INSTI-based regimens have achieved high rates of virologic suppression and often have greater tolerability than PI- or NNRTI-based regimens.
- In certain clinical situations, a PI- or an NNRTI-based regimen may be preferred. In recognition of these situations, a new category—called Recommended Initial Regimens in Certain Clinical Situations—has been added to the Guidelines.
- Darunavir (DRV)-based regimens have been moved to the category of Recommended Initial Regimens in Certain Clinical Situations based on trials showing improved outcomes with INSTI-based regimens when compared with ritonavir-boosted darunavir (DRV/r), in part because of greater tolerability of the former. An example of a situation in which a DRV-based regimen may still be preferred is when a high genetic barrier to resistance is particularly important, such as when there is substantial concern regarding a person's adherence or when antiretroviral therapy (ART) should be initiated before resistance test results are available. Other examples of important clinical considerations that may favor specific regimens are included in [Table 7](#).
- Recommended NRTI combinations continue to be ABC/3TC and one of the tenofovir products—TAF or TDF—with FTC. With additional data since the last revision, the relative advantages of the two available tenofovir formulations have become clearer. TAF has less bone and kidney toxicity than TDF and is therefore particularly advantageous in people with underlying bone and kidney disease or those at high risk for these conditions. TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. Safety, cost, and access are among the factors to consider in choosing between these two formulations of tenofovir. Guidance for the clinician on choosing between ABC-, TAF-, and TDF-containing regimens are featured in these guidelines.

## Table 6. Recommended Antiretroviral Regimens for Initial Therapy

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, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order. [Table 7](#) provides ARV recommendations based on specific clinical scenarios.

| <b>Recommended Initial Regimens for Most People with HIV</b>  |
|---|
| Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.   |
| <p><b>INSTI + 2 NRTIs:</b></p> <ul style="list-style-type: none"> <li>• DTG/ABC/3TC<sup>a</sup> (<b>AI</b>)—if HLA-B*5701 negative</li> <li>• DTG + tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>AI</b> for both TAF/FTC and TDF/FTC)</li> <li>• EVG/c/tenofovir<sup>b</sup>/FTC (<b>AI</b> for both TAF/FTC and TDF/FTC)</li> <li>• RAL<sup>c</sup> + tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>AI</b> for TDF/FTC, <b>All</b> for TAF/FTC)</li> </ul>  |
| <b>Recommended Initial Regimens in Certain Clinical Situations</b>  |
| These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see <a href="#">Table 7</a> for examples).   |
| <p><b>Boosted PI + 2 NRTIs:</b> (In general, boosted DRV is preferred over boosted ATV)</p> <ul style="list-style-type: none"> <li>• (DRV/c or DRV/r) + tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>AI</b> for DRV/r and <b>All</b> for DRV/c)</li> <li>• (ATV/c or ATV/r) + tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>BI</b>)</li> <li>• (DRV/c or DRV/r) + ABC/3TC<sup>a</sup> —if HLA-B*5701–negative (<b>BII</b>)</li> <li>• (ATV/c or ATV/r) + ABC/3TC<sup>a</sup> —if HLA-B*5701–negative and HIV RNA &lt;100,000 copies/mL (<b>CI</b> for ATV/r and <b>CIII</b> for ATV/c)</li> </ul> <p><b>NNRTI + 2 NRTIs:</b></p> <ul style="list-style-type: none"> <li>• EFV + tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>BI</b> for EFV/TDF/FTC and <b>BII</b> for EFV + TAF/FTC)</li> <li>• RPV/tenofovir<sup>b</sup>/FTC<sup>a</sup> (<b>BI</b>)—if HIV RNA &lt;100,000 copies/mL and CD4 &gt;200 cells/mm<sup>3</sup></li> </ul> <p><b>INSTI + 2 NRTIs:</b></p> <ul style="list-style-type: none"> <li>• RAL<sup>c</sup> + ABC/3TC<sup>a</sup> (<b>CII</b>)—if HLA-B*5701–negative and HIV RNA &lt; 100,000 copies/mL</li> </ul> <p>Regimens to Consider when ABC, TAF, and TDF Cannot be Used:<sup>d</sup></p> <ul style="list-style-type: none"> <li>• DRV/r + RAL (BID) (<b>CI</b>)—if HIV RNA &lt;100,000 copies/mL and CD4 &gt;200 cells/mm<sup>3</sup></li> <li>• LPV/r + 3TC<sup>a</sup> (BID)<sup>e</sup> (<b>CI</b>)</li> </ul> |

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

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

<sup>c</sup> RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.

<sup>d</sup> Several other NRTI-limiting treatment strategies are under investigation. See the section titled Selected Strategies That Are Under Evaluation and Not Yet Recommended below for discussion regarding these regimens.

<sup>e</sup> LPV/r plus 3TC is the only boosted PI plus 3TC regimen with published 48-week data in a randomized controlled trial in ART-naive patients. Limitations of LPV/r plus 3TC include twice-daily dosing, high pill burden, and greater rates of gastrointestinal side effects than other PIs.

**Note:** The following are available as coformulated drugs: 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; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BID = twice daily; CD4 = CD4 T lymphocyte; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate



## Selecting an Initial Antiretroviral Regimen

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

### *Choosing the Two Nucleoside Reverse Transcriptase Inhibitors*

All the **Recommended Initial Regimens for Most People with HIV and most of the Recommended Initial Regimens in Certain Clinical Situations** 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) and the fact that HLA-B\*5701 testing is not required for their use. Moreover, TDF has been associated with lower lipid levels than TAF and ABC. 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.<sup>4-6</sup> 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. 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. **For patients in whom ABC, TAF, or TDF cannot be used, recommendations for NRTI-limiting treatment regimens are given in [Table 6](#) and in the section below on Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used.**

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

The choice between an INSTI, PI, or NNRTI as the third drug in an initial ARV regimen should be guided by the regimen's efficacy, genetic barrier to resistance, adverse effects profile, and convenience. The patient's comorbidities, concomitant medications, and the potential for drug-drug interactions should also be considered (see [Tables 7](#) and [8](#) for guidance). The Panel's **Recommended Initial Regimens for Most People with HIV** as listed in [Table 6](#) include an INSTI plus two NRTIs. For most patients, an INSTI-containing regimen will be highly effective, have few adverse effects, and (with raltegravir [RAL] and dolutegravir [DTG]) have no significant CYP3A4-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.<sup>7-9</sup> **For these reasons, all three currently available INSTIs are included among the Recommended Initial Regimens for Most People with HIV.** An exception is in those individuals with uncertain adherence or in whom treatment needs to begin before resistance testing results are available (e.g., during acute HIV infection, pregnancy, and 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 patients experiencing virologic failure while on a DTG-containing initial regimen, and transmitted resistance has not yet been identified. Ritonavir-boosted atazanavir (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, a randomized clinical trial showed that ATV/r had a higher rate of adverse effect-associated drug discontinuation than DRV/r and RAL.<sup>7</sup> **In a substudy of this same trial, and in a separate cross-sectional cohort study, ATV/r use was associated with less progression of atherosclerosis as measured by carotid artery intima medial thickness.<sup>10,11</sup> Whether this finding will translate into a clinical benefit is uncertain. Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and ritonavir-boosted lopinavir [LPV/r]) and an increased risk of cardiovascular events, while this association was not seen with ATV.<sup>12-15</sup> Another**

observational cohort of predominantly male participants showed a lower rate of cardiovascular events in participants receiving ATV-containing regimens compared with other regimens.<sup>16</sup> Further study is needed.

NNRTI-based (efavirenz [EFV] or rilpivirine [RPV]) regimens may be optimal choices for some patients, although these drugs have low genetic barriers to resistance. EFV has a long track record of widespread use in the United States and globally, and its minimal PK interaction with rifamycins makes it an attractive option for patients who require concomitant treatment for tuberculosis (TB). Most EFV-based regimens have excellent virologic efficacy, including in patients with high HIV RNA (except when EFV is used with ABC/3TC); however, the relatively high rate of central nervous system (CNS)-related side effects makes EFV-based regimens less tolerable than other regimens. RPV has fewer adverse effects than EFV, is available as one of the smallest coformulated single tablets, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with high baseline HIV RNA (>100,000 copies/mL) and low CD4 count (<200 cells/mm<sup>3</sup>).

### ***Factors to Consider When Selecting an Initial Regimen***

When selecting a regimen for an individual person with HIV, a number of patient- and regimen-specific characteristics should be considered. The goal is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen for the patient in order to achieve sustained virologic control. Some of the factors can be grouped into the following categories:

#### Initial Characteristics to Consider in All Persons with HIV:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 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
- Individual preferences
- Anticipated adherence to the regimen

#### Specific Comorbidities or Other Conditions:

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

#### Regimen-Specific Considerations:

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

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

This table is designed to guide clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a person with HIV, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a person is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see [Table 8](#) for additional information regarding the advantages and disadvantages of particular ARV medications.

| Patient or Regimen Characteristics  | Clinical Scenario  | Consideration(s)  | Rationale/Comments  |
|-------------------------------------|--|---|---|
| <b>Pre-ART Characteristics</b>      | CD4 count <200 cells/mm <sup>3</sup>   | <b>Do Not Use the Following Regimens:</b><br>• RPV-based regimens<br>• DRV/r + RAL  | A higher rate of virologic failure has been observed in those with low pretreatment CD4 count.  |
|                                     | HIV RNA >100,000 copies/mL   | <b>Do Not Use the Following Regimens:</b><br>• RPV-based regimens<br>• ABC/3TC with EFV or ATV/r<br>• DRV/r + RAL   | Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA.   |
|                                     | HLA-B*5701–positive  | <b>Do not use ABC-containing regimens.</b>  | Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele.  |
|                                     | ARV must be started before HIV drug resistance results are available (e.g., in a person with acute HIV or when a rapid initiation of ART is warranted). See <a href="#">Initiation of Antiretroviral Therapy</a> . | <b>Avoid NNRTI-based regimens.</b><br><b>Recommended ART Regimens:</b><br>• (DRV/r or DRV/c) + tenofovir <sup>a</sup> /FTC; or<br>• DTG + tenofovir <sup>a</sup> /FTC | Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.<br><br>Resistance to DRV and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date.  |
| <b>ART-Specific Characteristics</b> | A one-pill, once-daily regimen is desired.   | <b>STR Options Include:</b><br>• DTG/ABC/3TC<br>• EFV/TDF/FTC<br>• EVG/c/TAF/FTC<br>• EVG/c/TDF/FTC<br>• RPV/TAF/FTC<br>• RPV/TDF/FTC                                 | Do not use RPV-based regimens if HIV RNA >100,000 copies/mL and CD4 count <200/mm <sup>3</sup> .<br><br>Since RPV-containing STRs are smaller in size than other STRs, they may be considered when a person has difficulty swallowing a larger pill.<br><br>Do not use DTG/ABC/3TC if patient is HLA-B*5701–positive.<br><br>See <a href="#">Appendix B, Table 7</a> for recommendations on ARV dose modification in the setting of renal impairment. |
|                                     | Food effects   | <b>Regimens that Can be Taken Without Regard to Food:</b><br>• RAL- or DTG-based regimens   | Oral bioavailability of these regimens is not significantly affected by food.   |



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

| Patient or Regimen Characteristics      | Clinical Scenario                                   | Consideration(s)   | Rationale/Comments   |
|---|---|--|--|
| ART-Specific Characteristics, continued | Food effects, continued                             | <u>Regimens that Should be Taken with Food:</u> <ul style="list-style-type: none"> <li>• ATV/r- or ATV/c-based regimens</li> <li>• DRV/r- or DRV/c-based regimens</li> <li>• EVG/c/TAF/FTC<sup>a</sup></li> <li>• EVG/c/TDF/FTC<sup>a</sup></li> <li>• RPV-based regimens</li> </ul>                 | Food improves absorption of these regimens. RPV-containing regimens should be taken with at least 390 calories of food.  |
|   |   | <u>Regimens that Should be Taken on an Empty Stomach:</u> <ul style="list-style-type: none"> <li>• EFV-based regimens</li> </ul>   | Food increases EFV absorption and may increase CNS side effects.   |
| Presence of Other Conditions            | Chronic kidney disease (defined as CrCl <60 mL/min) | <b>Avoid TDF.</b> Use ABC or TAF.<br>ABC may be used if HLA-B*5701–negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC + (EFV or ATV/r).<br>TAF may be used if CrCl >30 mL/min.<br>Consider avoiding ATV.  | TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction reported in patients using TDF in conjunction with RTV-containing regimens.<br>TAF has less impact on renal function and lower rates of proteinuria than TDF. |
|   |   | <u>Other Options When ABC or TAF Cannot be Used:</u> <ul style="list-style-type: none"> <li>• LPV/r + 3TC; or</li> <li>• RAL + DRV/r (if CD4 count &gt;200 cells/mm<sup>3</sup>, HIV RNA &lt;100,000 copies/mL)</li> <li>• See text for discussion of alternative NRTI-limiting regimens.</li> </ul> | ABC has not been associated with renal dysfunction.<br>See <a href="#">Appendix B, Table 7</a> for recommendations on ARV dose modification in patients with renal insufficiency.  |
|   |   | Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.   | Refer to <a href="#">Appendix B, Table 7</a> for specific dosing recommendations.<br>Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.   |
|   |   | <b>Avoid TDF.</b><br>Use ABC or TAF.<br>ABC may be used if HLA-B*5701–negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC + (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.                           |
|   | Psychiatric illnesses                               | <b>Consider avoiding EFV- and RPV-based regimens.</b><br>Patients on INSTI-based regimens with pre-existing psychiatric conditions should be closely monitored.  | EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality.<br>INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series.                                       |

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

| Patient or Regimen Characteristics                | Clinical Scenario   | Consideration(s)   | Rationale/Comments   |
|---|---|--|--|
| <b>Presence of Other Conditions,</b><br>continued | HIV-associated dementia (HAD)   | <b>Avoid EFV-based regimens if possible.</b><br><br>Favor DTG- or DRV-based regimens.  | EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms.<br><br>There is a theoretical CNS penetration advantage of DTG- or DRV-based regimens.  |
|   | Narcotic replacement therapy required   | <b>If patient is receiving methadone, consider avoiding EFV-based regimens.</b><br><br>If EFV is used, an increase in methadone dose may be necessary.   | EFV reduces methadone concentrations and may lead to withdrawal symptoms.  |
|   | High cardiac risk   | <b>DTG-, RAL- or RPV-based regimens may be advantageous in this setting.</b><br><br>Consider avoiding ABC- and LPV/r-based regimens.<br><br><b>If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen.</b> | An increased CV risk has been observed in some studies.<br><br>Observational cohort studies reported an association between some PIs (DRV, IDV, FPV, and LPV/r) and an increased risk of CV events, while this has not been seen with ATV (see text); further study is needed. |
|   | Cardiac QTc interval prolongation   | Consider avoiding EFV- or RPV-based regimens if taking other medications with known risk of torsades de pointes, or in patients at higher risk of torsades de pointes.   | High EFV or RPV concentrations may cause QT prolongation.  |
|   | Hyperlipidemia  | <u>The Following ARV Drugs Have Been Associated with Dyslipidemia:</u><br><br>• PI/r or PI/c<br>• EFV<br>• EVG/c   | <b>DTG, RAL, and RPV have fewer lipid effects.</b><br><br>TDF has been associated with lower lipid levels than ABC or TAF.   |
|   | Patients with history of poor adherence to ARV or inconsistent engagement in care | Consider boosted PI- or DTG-based regimens.  | These regimens have a high genetic barrier to resistance.  |
|   | Pregnancy   | Refer to the <a href="#">Perinatal Guidelines</a> for specific regimen recommendations.  |  |
| <b>Presence of Coinfections</b>                   | HBV infection   | Use TDF or TAF, with FTC or 3TC, whenever possible.<br><br><u>If TDF and TAF Are Contraindicated:</u><br>• For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see <a href="#">HBV/HIV Coinfection</a> ).                     | TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug active against HBV.   |
|   | HCV treatment required  | Refer to recommendations in <a href="#">HCV/HIV Coinfection</a> , with special attention to potential interactions between ARV drugs and HCV drugs.  |  |

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

| Patient or Regimen Characteristics  | Clinical Scenario                   | Consideration(s)  | Rationale/Comments   |
|-------------------------------------|-------------------------------------|---|--|
| Presence of Coinfections, continued | Treating TB disease with rifamycins | <p>TAF is <b>not recommended</b> with any rifamycin-containing regimen.</p> <p><u>If Rifampin is Used:</u></p> <ul style="list-style-type: none"> <li>• EFV can be used without dosage adjustment.</li> <li>• If RAL is used, increase RAL dose to 800 mg BID.</li> <li>• Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label).</li> </ul> <p>If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.</p> | <ul style="list-style-type: none"> <li>• Rifamycins may significantly reduce TAF exposure.</li> <li>• Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PIs, INSTIs, and RPV.</li> <li>• Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs.</li> <li>• Rifabutin is a less potent inducer and is an option for patients receiving non-EFV-based regimens.</li> </ul> <p>Refer to <a href="#">Tables 18a, b, d and e</a> for dosing recommendations for rifamycins used with different ARV agents.</p> |

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

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BID = twice daily; c = cobicistat; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = 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 or r = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase

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

## Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

### Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, either with the same<sup>17-19</sup> or a different (third) ARV drug (also see the discussion in the dolutegravir section).<sup>20</sup>

- 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.<sup>17</sup> 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.<sup>21</sup>
- 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.<sup>18</sup>
- 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.<sup>19</sup>

### 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 1,733 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.<sup>4</sup> At 144 weeks, TAF/FTC was superior to TDF/FTC (84.2% vs. 80% of participants achieved plasma HIV RNA <50 copies/mL, respectively), largely driven by a higher rate of treatment discontinuation in the TDF arm.<sup>22</sup>
  - Participants in the TAF arm had significantly smaller reductions in BMD at the spine and the hip than those in the TDF arm through 144 weeks.<sup>22</sup>
  - 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.<sup>23</sup> 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%,  $P < 0.001$ ).<sup>6</sup>
  - 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.<sup>24</sup>

- A phase 2 study of coformulated cobicistat-boosted DRV (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% vs. 74%) in treatment-naive patients.<sup>25</sup> Less proteinuria and less change in BMD were observed in the TAF arm.
- Combination TAF/FTC was also approved based on efficacy and safety data from one switch study in virologically suppressed patients.<sup>5</sup> This study included 663 patients with HIV 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 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 log<sub>10</sub> IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.<sup>26</sup> 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<sub>10</sub> 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.<sup>26</sup>

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

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

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.<sup>20,27-29</sup>

#### 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.<sup>30,31</sup> 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 (i.e., within 6 months) or current use of ABC was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.<sup>13,32</sup>
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and



cardiovascular events. Some studies have found an association.<sup>33-40</sup> Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.<sup>12,41-44</sup>

- 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 and as a coformulated tablet in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No 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 DTG/ABC/3TC as a fixed-dose combination, the Panel classifies DTG/ABC/3TC as a Recommended Initial Regimen for Most People with HIV (**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, DRV/c, DRV/r, 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 tenofovir (TFV), is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

#### Adverse Effects

##### *Renal and Bone Effects:*

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

##### *Lipid Effects:*

- In the randomized controlled trials in ART-naïve patients, as well as in switch studies (described below), levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and TDF. **The clinical significance of this finding is not clear.**<sup>4-6</sup>

#### 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  $\geq 30$  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 Patients with HIV 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](#)).<sup>26</sup>

#### The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,<sup>45</sup> and its availability as a component of various fixed-dose combinations, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with DTG (**AI**), EVG/c (**AI**), and RAL (**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.<sup>46,47-55</sup>

#### Adverse Effects

##### *Renal Effects:*

- New onset or worsening renal impairment has been associated with TDF use.<sup>56,57</sup> Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females)<sup>58</sup> and pre-existing renal impairment.<sup>59</sup> 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. As previously noted, adverse effects on renal biomarkers such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.<sup>57,59-63</sup>

##### *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.<sup>64,65</sup> 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.<sup>66</sup>

#### 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 Patients with HIV Receiving Antiretroviral Therapy](#)). In patients who have pre-existing renal insufficiency (creatinine clearance [CrCl]  $< 60$  mL/min),<sup>67</sup> 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 fixed dose combination drugs, the Panel considers TDF/FTC a Recommended NRTI combination for initial ART in most persons with HIV when combined with DTG, EVG/c, or RAL. 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 ARV-naïve patients with HIV. 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. **INSTI-based regimens are Recommended Initial Regimens for Most People with HIV.**

### ***Integrase Strand Transfer Inhibitor-Based Regimens*** (In alphabetical order)

#### **Dolutegravir (DTG)**

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

#### Efficacy in Clinical Trials:

The efficacy of DTG in treatment-naïve patients has been evaluated in several fully powered randomized controlled clinical trials. 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 two-NRTI regimen, either ABC/3TC or TDF/FTC, to 822 participants. At week 96, DTG was noninferior to RAL.<sup>55</sup>
  - 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.<sup>20</sup> At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.<sup>68</sup>
- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to DRV/r 800/100 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.<sup>69,70</sup> 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.<sup>71</sup>
- The ARIA trial is an open-label, phase 3b randomized controlled trial, comparing the efficacy and safety of DTG/ABC/3TC to ATV/r plus TDF/FTC in ART-naïve, nonpregnant women. At week 48, 82% of participants in the DTG group achieved HIV RNA viral loads <50 copies/mL compared with 71% in the ATV group ( $P = 0.005$ ). The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.<sup>72</sup>

### Adverse Effects:

- DTG is generally well tolerated. The most common adverse reactions of moderate to severe intensity with an incidence  $\geq 2\%$  in the clinical trials were insomnia and headache. Cases of HSRs were reported in  $<1\%$  of trial participants.
- Case series of neuropsychiatric adverse events (sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.<sup>73,74</sup> Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs.<sup>75,76</sup> However, analyses of data from large randomized controlled trials as well as a health care database demonstrated similar rates of neuropsychiatric adverse events with DTG-based regimens versus other ARV regimens,<sup>77</sup> with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs,<sup>78</sup> and not only DTG. Further studies will be needed to precisely clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric adverse events has not been defined.

### 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 fewer drug interactions than EVG/c. See Drug Interactions for specific drug-drug interactions which require dosage adjustment.
- 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 as part of a three-drug regimen 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 (**AI**), or TDF/FTC (**AI**) as a **Recommended Initial Regimen for Most People with HIV**.

### **Elvitegravir (EVG)**

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

### 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.<sup>79</sup>
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.<sup>80</sup>
  - In a randomized, blinded trial performed in women with HIV, EVG/c/TDF/FTC had superior efficacy when compared to ATV/r plus TDF/FTC, in part because of a lower rate of treatment discontinuation.<sup>9</sup>

- 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  $\geq 50$  mL/min.<sup>4,24</sup>
  - At 48 and 96 weeks, TAF was noninferior to TDF when both were combined with EVG/c/FTC, whereas EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC at 144 weeks.<sup>22</sup>

#### Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.<sup>79,80</sup>
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.<sup>81</sup>
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see discussion under DTG).

#### Other Factors and Considerations:

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI inhibits CYP3A, it interacts with a number of medications that are metabolized by this enzyme (see [Drug Interactions](#)).<sup>82</sup>
- EVG plasma concentrations are lower when it is administered simultaneously with polyvalent cation-containing antacids or supplements (see [Drug Interactions](#)). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG dosing.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.<sup>83</sup> 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.<sup>63</sup>
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl  $< 70$  mL/min.<sup>63</sup>
- EVG/c/TAF/FTC **is not recommended** for patients with pretreatment estimated CrCl  $< 30$  mL/min.
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-treated patients whose therapy failed.<sup>79,80</sup> These mutations conferred cross-resistance to RAL, with most retaining susceptibility to DTG.

#### The Panel's Recommendation:

- On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as Recommended Initial Regimens for Most People with HIV (AI). EVG/c/TAF/FTC should only be used in people with estimated CrCl  $\geq 30$  mL/min; EVG/c/TDF/FTC should only be used in people with estimated CrCl  $\geq 70$  mL/min.

### **Raltegravir (RAL)**

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

#### Efficacy in Clinical Trials

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

- The efficacy of RAL **at a dose of 400 mg twice daily** (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials, and a third open-label randomized trial.
  - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.<sup>51</sup> RAL was superior to EFV at 4 and 5 years,<sup>54,84</sup>



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 nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 and 125 participants with baseline viral loads  $\geq 100,000$  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.<sup>55</sup>
- ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens containing RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the ritonavir-boosted protease inhibitor (PI/r) arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.<sup>7</sup>

#### *RAL 1200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:*

- In a phase 3, randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.<sup>85</sup>

#### Adverse Effects:

- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.<sup>86</sup>
- Neuropsychiatric adverse events (for example, insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see discussion under DTG).<sup>77,87</sup>

#### Other Factors and Considerations:

- RAL can be administered as 1200 mg (two 600-mg tablets) once a day or as 400 mg twice daily with or without food in ART-naïve patients.
- Coadministration of RAL as either 400 mg twice daily or 1200 mg once daily with aluminum- and/or magnesium-containing antacids **is not recommended**. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See [Table 18d](#) for dosing recommendations.
- RAL has a lower genetic barrier to resistance than RTV-boosted PIs and DTG.

#### The Panel's Recommendations:

- On the basis of these clinical trial data, the Panel considers RAL **given as 1200 mg (two 600-mg tablets) once daily or as 400 mg twice daily** plus TDF/FTC (**AI**) or TAF/FTC (**AII**) as a **Recommended Initial Regimen for Most People with HIV**.
- Because fewer patients have received RAL plus ABC/3TC in clinical trials or practice and there has not been a randomized trial comparing ABC/3TC plus RAL to TDF/FTC plus RAL, the Panel categorizes RAL plus ABC/3TC as a **Recommended Initial Regimen in Certain Clinical Situations** (**BII**).

## 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<sup>88</sup> 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.<sup>89,90</sup> EFV- and RPV-based regimens are now categorized as **Recommended Initial Regimens in Certain Clinical Situations** 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 pretreatment viral loads (>100,000 copies/mL) or low CD4 counts (<200 cells/mm<sup>3</sup>) 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.<sup>91</sup>
- 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.<sup>92</sup>
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.<sup>79</sup>

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.<sup>20</sup>
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks.<sup>51</sup> RAL was superior to EFV at 4 and 5 years,<sup>54,84</sup> 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.<sup>93</sup>

ENCORE 1, a multinational randomized placebo-controlled trial, compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg (reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.<sup>94</sup> 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, it is not coformulated in a fixed-dose combination tablet, and data for its use in pregnancy and in patients with TB/HIV coinfection are lacking.

#### Adverse Effects:

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression), which resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur. An analysis of four 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.<sup>95</sup> This association, however, was not found in analyses of three large observational cohorts,<sup>96,97</sup> or in a retrospective cohort study that used U.S. administrative pharmacy claims data.<sup>98</sup>
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.<sup>99,100</sup> Consider an alternative therapy to EFV in patients taking medications known to increase the risk of torsades de pointes, or in patients at higher risk of torsades de pointes.

#### Other Factors and Considerations:

- EFV is formulated both as a single-drug 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 18b](#), [19a](#), and [19b](#)).
- 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.<sup>101</sup> A link between EFV and birth defects in humans has not been supported in meta-analyses (see the [Perinatal Guidelines](#)).<sup>102</sup>
- Because EFV has been associated with depression and suicidality, screening for antenatal and postpartum depression in women with HIV who are taking a regimen that includes EFV is recommended.

#### 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 Recommended Initial Regimens in Certain Clinical Situations.
- EFV at a reduced dose has not been studied in the U.S. population, in pregnant women, or in patients with TB/HIV coinfection. The Panel **cannot recommend** the use of reduced-dose EFV.

### **Rilpivirine (RPV)**

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

#### Efficacy in Clinical Trials:

Two phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.<sup>92</sup> 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 participants than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with

virologic failure, NNRTI and NRTI resistance was more frequently identified in those treated with RPV.

- Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 counts <200 cells/mm<sup>3</sup> than in those with CD4 counts ≥200 cells/mm<sup>3</sup>.

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. **The results at 96 weeks<sup>103</sup> were similar to the findings reported at 48 weeks.**<sup>93</sup>

- 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, participants taking the coformulated drug had plasma concentrations of RPV, FTC, and TAF 25 mg that were similar to concentrations seen in participants who received RPV as the single-tablet formulation and TAF/FTC when given as part of the fixed-dose combination of EVG/c/TAF 10 mg/FTC.<sup>45</sup>

#### 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. However, up to 9% of clinical trial participants experienced depressive disorders, including approximately 1% of participants who had suicidal thoughts or who attempted suicide. Patients with severe depressive symptoms should be evaluated to assess whether symptoms may be due to RPV and if the risks of 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-tablet 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 (containing 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 H<sub>2</sub> 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 **Recommended Initial Regimens in Certain Clinical Situations**.
- Use of RPV with TAF/FTC (**BII**) or TDF/FTC (**BI**) should be limited to ART-naive patients with

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

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

## Protease Inhibitor-Based Regimens

### Summary

FDA-approved PIs include ATV, ATV/c, DRV, DRV/c, FPV, IDV, LPV/r, nelfinavir (NFV), RTV, saquinavir (SQV), and tipranavir (TPV). PI-based regimens with PK enhancement have demonstrated virologic potency, durability in treatment-naïve 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.<sup>104,105</sup> 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 CYP3A4 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 PIs are listed in [Table 8](#) and [Appendix B, Table 3](#).

PIs that are recommended for use in ART-naïve 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, DRV/c, ATV/c, or ATV/r together with two NRTIs as PI-based regimen options in the category of Recommended Initial Regimens in Certain Clinical Situations. 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, mainly hyperbilirubinemia, was greater in the ATV/r arm than in the other two arms.<sup>7</sup>

Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events, while this was not seen with ATV.<sup>12-14,106</sup> Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens compared with other regimens.<sup>16</sup> Further study is needed.

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 two NRTIs 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 ART regimens with fewer toxicities. DRV/r plus twice daily RAL or LPV/r plus 3TC are regimens to be considered when ABC, TAF, or TDF cannot be used (see below). 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.

### 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,<sup>49</sup> and superior at week 192.<sup>107</sup> 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 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.<sup>8</sup>
- 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.<sup>7</sup>

#### 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.<sup>7</sup> 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 ( $P \leq 0.02$ ).<sup>108</sup>
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.<sup>106</sup>

#### 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 Recommendations:

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

#### **Darunavir/Cobicistat (DRV/c)**

A combination of DRV 800 mg with COBI 150 mg is bioequivalent to DRV 800 mg with RTV 100 mg in healthy volunteers based on the maximum concentration and area under the concentration time curve for DRV.<sup>109</sup> Because the minimum concentration ( $C_{\min}$ ) of DRV combined with COBI was 31% lower than that with DRV combined with RTV, bioequivalence for the  $C_{\min}$  was not achieved.<sup>110</sup>

#### Efficacy in Clinical Trials:

- In a single-arm trial of treatment-naive (94%) and treatment-experienced (6%) patients, the coformulated DRV/c 800/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.<sup>111</sup>
- A phase 2 study of coformulated DRV/c plus TAF/FTC versus DRV/c plus TDF/FTC demonstrated similar virologic suppression rates in both arms (75% and 74%, respectively) in treatment-naive patients.<sup>25</sup> Less proteinuria and less change in bone mineral density were observed in the TAF arm.

### Adverse Effects:

- The most common treatment-emergent adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease;<sup>106</sup> data on DRV/c are too limited to draw conclusions.

### 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 Recommended Initial Regimens in Certain Clinical Situations.
- DRV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

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

#### Efficacy in Clinical Trials:

- 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 two regimens showed similar virologic and CD4 responses at 96 weeks.<sup>112</sup>
- 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.<sup>91</sup> 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.<sup>113</sup>
- 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.<sup>80</sup> A phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.<sup>9</sup> At week 48, the virologic suppression rate in the EVG/c arm was superior to the ATV/r arm. Nineteen women in the PI arm discontinued therapy because of adverse events, compared to five women in the INSTI arm.
- In 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.<sup>7</sup>
- In the Gilead Study 114, all patients received TDF/FTC and ATV, and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.<sup>114</sup> 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.<sup>115</sup>
- In a phase 3 trial, 499 ART-naive women were randomized to either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, DTG was found to be noninferior to ATV/r in rate of virologic suppression (<50 copies/mL) and fewer drug-related adverse events occurred in the DTG arm.<sup>72</sup>

### 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.<sup>116</sup>

- Nephrolithiasis,<sup>117-119</sup> nephrotoxicity,<sup>15</sup> and cholelithiasis<sup>120</sup> 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, H<sub>2</sub> antagonists, and particularly proton pump inhibitors) may impair absorption of ATV. [Table 18a](#) 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).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events, while this was not seen with ATV.<sup>12-14,106</sup> Another study of an observational cohort of predominantly male participants found a lower rate of CV events in participants receiving ATV-containing regimens compared with participants receiving other regimens.<sup>16</sup> Further study is needed.

#### The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC (**BII**) or TDF/FTC (**BI**) as **Recommended Initial Regimens in Certain Clinical Situations**.
- ATV/r or ATV/c may be used with ABC/3TC in patients whose pre-ART HIV RNA <100,000 copies/mL (**CI** for ATV/r and **CIII** for ATV/c).
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

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

All currently Recommended ARV regimens consist of two NRTIs plus a third active drug. This strategy, however, may not be possible or optimal in all patients. In some situations, it may be necessary to avoid ABC, TAF, and TDF, such as in 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 two NRTIs or the NRTI drug class altogether. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of patients with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

### **Strategies with Good Supporting Evidence**

#### **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 (800/100 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 count <200 cells/mm<sup>3</sup>, however, there were more failures in the two-drug arm; a trend towards more failure was also observed for those with pretreatment HIV RNA ≥100,000 copies/mL.<sup>121</sup> 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.<sup>122,123</sup>
- 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 counts >200 cells/mm<sup>3</sup>, 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 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 noninferiority criteria. The LPV/r plus 3TC regimen was better tolerated than the LPV/r plus two NRTI regimen.<sup>124</sup>
- This regimen is used infrequently given the requirement of twice-daily dosing, the relatively high pill burden (a total of 5–6 tablets per day), and the side effect profile of LPV/r. In view of 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 **and in whom other alternatives cannot be used (CI)**.

### ***Selected Strategies That Are Under Evaluation and Not Yet Recommended***

Several other treatment regimens for ART-naive patients who cannot use ABC, TAF, and TDF are currently under investigation. As the current data supporting these regimens are limited to single-arm studies or interim analyses of ongoing trials, these regimens cannot yet be recommended. However, some experts may consider these regimens when a patient cannot safely receive ABC, TAF, or TDF. If these treatment strategies are used, patients should be closely monitored to assure viral suppression is achieved and maintained. Two selected strategies are listed below.

#### **Dolutegravir plus Lamivudine (DTG plus 3TC)**

- The PADDLE trial was a small, single-arm study of DTG plus 3TC in 20 ART-naive adults with baseline HIV RNA <100,000 copies/mL. At 48 weeks, 18/20 (90%) subjects achieved HIV RNA <50 copies/mL.<sup>125</sup> Fifteen of these 18 participants completed 96 weeks of treatment and maintained HIV RNA <50 copies/mL.<sup>126</sup>
- The ACTG A5353 trial evaluated this same regimen in a single-arm trial that included ART-naive participants with a baseline HIV RNA of up to 500,000 copies/mL and no genotypic NRTI, INSTI, or PI resistance. The trial enrolled 120 participants; 37 (30.8%) participants had a baseline HIV RNA >100,000 copies/mL. At week 24, 90% of participants had HIV RNA <50 copies/mL; there were similar response rates in participants with baseline HIV RNA >100,000 copies/mL and ≤100,000 copies/mL (89% and 90%, respectively). Three participants experienced virologic failure, all of whom had suboptimal adherence (one developed an integrase gene-associated mutation).<sup>127</sup>
- Two phase 3 trials (GEMINI 1 and 2) comparing DTG plus 3TC to a three-drug regimen of DTG plus TDF/FTC in treatment-naive people with HIV are currently ongoing.

#### **Darunavir/ritonavir plus Lamivudine (DRV/r plus 3TC)**

- In the ANDES trial, 145 participants were randomized 1:1 to receive either open-label dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus 3TC/TDF. The median baseline HIV RNA was 4.5 log<sub>10</sub> copies, and 24% of subjects had HIV RNA >100,000 copies/mL. The trial is still ongoing, but an intention-to-treat snapshot analysis performed at week 24 showed that 71/75 (95%) subjects in the dual-therapy arm and 68/70 (97%) subjects in the triple-therapy arm achieved HIV RNA <400 copies/mL. By week 24, four subjects in the dual-therapy arm and one subject in the triple-therapy arm had discontinued treatment for reasons other than virologic failure. Virologic failure was documented in one subject in the triple-therapy arm. The investigators intend to enroll an additional 190 patients to power the study for a noninferiority assessment at the primary (week 48) virologic endpoint.<sup>128</sup>

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy** (page 1 of 4)

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

| ARV Class | ARV Agent(s) | Advantage(s)   | Disadvantage(s)  |
|-----------|--------------|--|--|
| Dual-NRTI | ABC/3TC      | <ul style="list-style-type: none"> <li>• Coformulated with DTG</li> </ul>  | <ul style="list-style-type: none"> <li>• May cause life-threatening HSRs in patients positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use.</li> <li>• In the ACTG 5202 study, patients with baseline HIV RNA <math>\geq 100,000</math> 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.</li> <li>• ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.</li> </ul>   |
|           | TAF/FTC      | <ul style="list-style-type: none"> <li>• Coformulated with EVG/c or RPV</li> <li>• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection</li> <li>• Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than after initiation of TDF/FTC</li> <li>• Approved for patients with eGFR <math>\geq 30</math> mL/min</li> </ul>   | <ul style="list-style-type: none"> <li>• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids.</li> </ul>   |
|           | TDF/FTC      | <ul style="list-style-type: none"> <li>• Coformulated with EFV, EVG/c, and RPV as STRs</li> <li>• Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection</li> <li>• Better virologic responses than with ABC/3TC in patients with baseline viral load <math>\geq 100,000</math> copies/mL when combined with ATV/r or EFV</li> <li>• Associated with lower lipid levels than ABC or TAF</li> </ul> | <ul style="list-style-type: none"> <li>• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency</li> <li>• Osteomalacia has been reported as a consequence of proximal tubulopathy.</li> <li>• Decreases BMD more than other NRTI combinations</li> </ul>   |
| INSTI     | DTG          | <ul style="list-style-type: none"> <li>• Higher barrier to resistance than EVG or RAL</li> <li>• Coformulated with ABC and 3TC</li> <li>• No food requirement</li> <li>• No CYP3A4 interactions</li> <li>• Favorable lipid profile</li> </ul>  | <ul style="list-style-type: none"> <li>• Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in <a href="#">Table 18d</a>.</li> <li>• Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function</li> <li>• UGT substrate; potential for drug interactions (see <a href="#">Table 18d</a>)</li> <li>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)</li> </ul> |



**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy** (page 2 of 4)

| ARV Class        | ARV Agent(s) | Advantage(s)  | Disadvantage(s)  |
|------------------|--------------|---|--|
| INSTI, continued | EVG/c        | <ul style="list-style-type: none"> <li>• Coformulated with TDF/FTC or TAF/FTC</li> <li>• Compared with ATV/r, causes smaller increases in total and LDL cholesterol</li> </ul>  | <ul style="list-style-type: none"> <li>• EVG/c/TDF/FTC is only recommended for patients with baseline CrCl <math>\geq</math>70 mL/min; this regimen should be discontinued if CrCl decreases to <math>&lt;</math>50 mL/min.</li> <li>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</li> <li>• Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in <a href="#">Table 18d</a>.</li> <li>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.</li> <li>• Lower genetic barrier to resistance than boosted PI- or DTG-based regimens</li> <li>• Food requirement</li> <li>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)</li> </ul> |
|                  | RAL          | <ul style="list-style-type: none"> <li>• Compared to other INSTIs, has longest post-marketing experience</li> <li>• No food requirement</li> <li>• No CYP3A4 interactions</li> <li>• Favorable lipid profile</li> </ul> | <ul style="list-style-type: none"> <li>• Lower genetic barrier to resistance than boosted PI- or DTG-based regimens</li> <li>• Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported.</li> <li>• Rare cases of severe HSRs (including SJS and TEN) have been reported.</li> <li>• Higher pill burden than other INSTI-based regimens</li> <li>• No fixed-dose combination formulation</li> <li>• Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in <a href="#">Table 18d</a>.</li> <li>• UGT substrate; potential for drug interactions (see <a href="#">Table 18d</a>)</li> <li>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions)</li> </ul>   |

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy** (page 3 of 4)

| ARV Class | ARV Agent(s)   | Advantage(s)   | Disadvantage(s)   |
|-----------|----------------|--|---|
| NNRTIs    | EFV            | <ul style="list-style-type: none"> <li>• Coformulated with TDF/FTC</li> <li>• Long-term clinical experience</li> <li>• EFV-based regimens (except for EFV + ABC/3TC) have well-documented efficacy in patients with high HIV RNA.</li> </ul>   | <ul style="list-style-type: none"> <li>• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality</li> <li>• Teratogenic in nonhuman primates</li> <li>• Dyslipidemia</li> <li>• Rash</li> <li>• QTc interval prolongation; consider an alternative to EFV in patients taking medications with known risk of causing TdP, or in those at higher risk of TdP.</li> <li>• Transmitted resistance more common than with PIs and INSTIs</li> <li>• Greater risk of resistance at the time of treatment failure than with PIs</li> <li>• Potential for CYP450 drug interactions (see <a href="#">Tables 18b</a> and <a href="#">19a</a>)</li> <li>• Should be taken on an empty stomach (food increases drug absorption and CNS toxicities)</li> </ul>   |
|           | RPV            | <ul style="list-style-type: none"> <li>• Coformulated with TDF/FTC and TAF/FTC</li> <li>• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill size than other coformulated ARV drugs</li> <li>• Compared with EFV: <ul style="list-style-type: none"> <li>• Fewer CNS adverse effects</li> <li>• Fewer lipid effects</li> <li>• Fewer rashes</li> </ul> </li> </ul>  | <ul style="list-style-type: none"> <li>• <b>Not recommended</b> in patients with pre-ART HIV RNA &gt;100,000 copies/mL or CD4 count &lt;200 cells/mm<sup>3</sup> because of higher rate of virologic failure in these patients</li> <li>• Depression and suicidality</li> <li>• QTc interval prolongation; consider an alternative to RPV in patients taking medications with known risk of causing TdP, or in those at higher risk of TdP.</li> <li>• Rash</li> <li>• Transmitted resistance more common than with PIs and INSTIs</li> <li>• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimen containing EFV and 2 NRTIs</li> <li>• Potential for CYP450 drug interactions (see <a href="#">Tables 18b</a> and <a href="#">19a</a>)</li> <li>• Meal requirement (&gt;390 kcal)</li> <li>• Requires acid for adequate absorption <ul style="list-style-type: none"> <li>• Contraindicated with PPIs</li> <li>• Use with H2 antagonists or antacids with caution (see <a href="#">Table 18a</a> for detailed dosing information).</li> </ul> </li> </ul> |
| PIs       | ATV/c or ATV/r | <ul style="list-style-type: none"> <li>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL</li> <li>• PI resistance at the time of treatment failure uncommon with PK-enhanced PIs</li> <li>• ATV/c and ATV/r have similar virologic activity and toxicity profiles</li> <li>• Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events, while this has not been seen with ATV. Further study is needed. See text for discussion.</li> </ul> | <ul style="list-style-type: none"> <li>• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice</li> <li>• Food requirement</li> <li>• Absorption depends on food and low gastric pH (see <a href="#">Table 18a</a> for interactions with H2 antagonists, antacids, and PPIs)</li> <li>• Nephrolithiasis, cholelithiasis, nephrotoxicity</li> <li>• GI adverse effects</li> <li>• CYP3A4 inhibitors and substrates: potential for drug interactions (see <a href="#">Table 18a</a>)</li> </ul>  |

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy** (page 4 of 4)

| ARV Class      | ARV Agent(s)                       | Advantage(s)   | Disadvantage(s)   |
|----------------|------------------------------------|--|---|
| PIs, continued | ATV/c<br>(Specific considerations) | <ul style="list-style-type: none"> <li>• Coformulated tablet</li> </ul>  | <ul style="list-style-type: none"> <li>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.</li> <li>• Coadministration with TDF <b>is not recommended</b> in patients with CrCl &lt;70 mL/min</li> <li>• Less long-term clinical experience than for ATV/r</li> <li>• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</li> </ul>   |
|                | DRV/c or DRV/r                     | <ul style="list-style-type: none"> <li>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL</li> <li>• PI resistance at the time of treatment failure uncommon with PK-enhanced PIs</li> </ul> | <ul style="list-style-type: none"> <li>• Skin rash</li> <li>• Food requirement</li> <li>• GI adverse effects</li> <li>• CYP3A4 inhibitors and substrates: potential for drug interactions (see <a href="#">Table 18a</a>)</li> <li>• <b>Increased CV risk in one observational cohort study</b></li> </ul>  |
|                | DRV/c<br>(Specific considerations) | <ul style="list-style-type: none"> <li>• Coformulated tablet</li> </ul>  | <ul style="list-style-type: none"> <li>• Less long-term clinical experience than for DRV/r</li> <li>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.</li> <li>• Coadministration with TDF <b>is not recommended</b> in patients with CrCl &lt;70 mL/min</li> <li>• 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</li> <li>• COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.</li> </ul> |
|                | LPV/r                              | <ul style="list-style-type: none"> <li>• Only RTV-coformulated PI</li> <li>• No food requirement</li> </ul>  | <ul style="list-style-type: none"> <li>• Requires 200 mg per day of RTV</li> <li>• Possible higher risk of MI associated with cumulative use of LPV/r</li> <li>• 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.</li> <li>• Possible nephrotoxicity</li> <li>• CYP3A4 inhibitors and substrates: potential for drug interactions (see <a href="#">Table 18a</a>)</li> </ul>  |

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

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

| ARV Components or Regimens  | Reasons for <b>Not</b> Recommending as Initial Therapy   |
|---|--|
| <b>NRTIs</b>  |  |
| <b>ABC/3TC/ZDV (Coformulated)</b><br>As triple-NRTI combination regimen | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> </ul>  |
| <b>ABC/3TC/ZDV + TDF</b><br>As quadruple-NRTI combination regimen       | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> </ul>  |
| <b>d4T + 3TC</b>  | <ul style="list-style-type: none"> <li>• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)</li> </ul>                                      |
| <b>ddl + 3TC (or FTC)</b>   | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> <li>• Limited clinical trial experience in ART-naive patients</li> <li>• ddl toxicities such as pancreatitis and peripheral neuropathy</li> </ul>  |
| <b>ddl + TDF</b>  | <ul style="list-style-type: none"> <li>• High rate of early virologic failure</li> <li>• Rapid selection of resistance mutations</li> <li>• Potential for immunologic nonresponse/CD4 cell decline</li> <li>• Increased ddl drug exposure and toxicities</li> </ul>                  |
| <b>ZDV/3TC</b>  | <ul style="list-style-type: none"> <li>• 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</li> </ul> |
| <b>NNRTIs</b>   |  |
| <b>DLV</b>  | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> <li>• Inconvenient (three times daily) dosing</li> </ul>   |
| <b>ETR</b>  | <ul style="list-style-type: none"> <li>• Insufficient data in ART-naive patients</li> </ul>  |
| <b>NVP</b>  | <ul style="list-style-type: none"> <li>• Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including SJS and TEN)</li> <li>• When compared to EFV, NVP did not meet noninferiority criteria</li> </ul>   |
| <b>PIs</b>  |  |
| <b>ATV (Unboosted)</b>  | <ul style="list-style-type: none"> <li>• Less potent than boosted ATV</li> </ul>   |
| <b>DRV (Unboosted)</b>  | <ul style="list-style-type: none"> <li>• Use without RTV or COBI has not been studied</li> </ul>   |
| <b>FPV (Unboosted)</b><br>or<br><b>FPV/r</b>                            | <ul style="list-style-type: none"> <li>• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV</li> <li>• Less clinical trial data for FPV/r than for other RTV-boosted PIs</li> </ul>                       |
| <b>IDV (Unboosted)</b>  | <ul style="list-style-type: none"> <li>• Inconvenient dosing (three times daily with meal restrictions)</li> <li>• Fluid requirement</li> <li>• IDV toxicities such as nephrolithiasis and crystalluria</li> </ul>   |
| <b>IDV/r</b>  | <ul style="list-style-type: none"> <li>• Fluid requirement</li> <li>• IDV toxicities such as nephrolithiasis and crystalluria</li> </ul>   |
| <b>LPV/r + 2 NRTIs</b>  | <ul style="list-style-type: none"> <li>• Higher pill burden than other PI-based regimens</li> <li>• Higher ritonavir dose than other PI-based regimens</li> <li>• GI intolerance</li> </ul>  |
| <b>NFV</b>  | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> <li>• Diarrhea</li> </ul>  |
| <b>RTV as sole PI</b>   | <ul style="list-style-type: none"> <li>• High pill burden</li> <li>• GI intolerance</li> <li>• Metabolic toxicity</li> </ul>   |

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

| ARV Components or Regimens | Reasons for <b>Not</b> Recommending as Initial Therapy  |
|----------------------------|---|
| <b>PIs, continued</b>      |   |
| <b>SQV (Unboosted)</b>     | <ul style="list-style-type: none"> <li>• Inadequate bioavailability</li> <li>• Inferior virologic efficacy</li> </ul>   |
| <b>SQV/r</b>               | <ul style="list-style-type: none"> <li>• High pill burden</li> <li>• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG</li> </ul>   |
| <b>TPV/r</b>               | <ul style="list-style-type: none"> <li>• Inferior virologic efficacy</li> <li>• Higher rate of adverse events than other RTV-boosted PIs</li> <li>• Higher dose of RTV required for boosting than other RTV-boosted PIs</li> </ul>      |
| <b>CCR5 Antagonist</b>     |   |
| <b>MVC</b>                 | <ul style="list-style-type: none"> <li>• Requires testing for CCR5 tropism before initiation of therapy</li> <li>• No virologic benefit when compared with other recommended regimens</li> <li>• Requires twice-daily dosing</li> </ul> |

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

## References

1. Moore RD, Bartlett JG. Dramatic decline in the HIV-1 RNA level over calendar time in a large urban HIV practice. *Clin Infect Dis*. 2011;53(6):600-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21844006>.
2. Gill VS, Lima VD, Zhang W, et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clin Infect Dis*. 2010;50(1):98-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19951169>.
3. Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PloS one*. 2014;9(5):e97482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24830290>.
4. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.
5. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *The Lancet HIV*. 2016;3(4):e158-165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27036991>.
6. Wohl D, Thalme A, Finlayson R, et al. Renal safety of tenofovir alafenamide in patients at high risk of kidney disease. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: <http://www.croiconference.org/sessions/renal-safety-tenofovir-alafenamide-patients-high-risk-kidney-disease>.
7. Lennox JL, Landovitz RJ, Ribaud HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285539>.
8. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naïve adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *The Lancet HIV*. 2015;2(4):e127-136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26424673>.
9. Squires K, Kityo C, Hodder S, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected



- women (WAVES): a randomised, controlled, double-blind, phase 3 study. *The Lancet HIV*. 2016;3(9):e410-e420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27562742>.
10. Stein JH, Ribaud H, Hodis HN, et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness. *AIDS*. 2015;29(14):1775-1783. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26372383>.
  11. de Saint-Martin L, Bressollette L, Perfezou P, et al. Impact of atazanavir-based HAART regimen on the carotid intima-media thickness of HIV-infected persons: a comparative prospective cohort. *AIDS*. 2010;24(18):2797-2801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21063175>.
  12. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. 2010;170(14):1228-1238. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20660842>.
  13. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20039804>.
  14. Monforte AD, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. *AIDS*. 2013;27(3):407-415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23291539>.
  15. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis*. 2013;207(9):1359-1369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23382571>.
  16. LaFleur J, Bress AP, Rosenblatt L, et al. Cardiovascular outcomes among HIV-infected veterans receiving atazanavir. *AIDS*. 2017;31(15):2095-2106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28692532>.
  17. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19952143>.
  18. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *Journal of Acquired Immune Deficiency Syndromes*. 2010;55(1):49-57. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20431394>.
  19. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19542866>.
  20. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24195548>.
  21. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis*. 2011;204(8):1191-1201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21917892>.
  22. Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2017;75(2):211-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28282300>.
  23. Rijnders BJ, Post FA, Rieger A, et al. Longer-term renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: <http://www.croiconference.org/sessions/longer-term-renal-safety-tenofovir-alafenamide-vs-tenofovir-disoproxil-fumarate>.
  24. Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *Journal of Acquired Immune Deficiency Syndromes*. 2016;72(1):58-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26829661>.
  25. Mills A, Crofoot GJ, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. *Journal of Acquired Immune*

26. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfecting adults. *Journal of Acquired Immune Deficiency Syndromes*. 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27171740>.
27. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis*. 2004;39(7):1038-1046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15472858>.
28. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *Journal of Acquired Immune Deficiency Syndromes*. 2004;35(1):22-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14707788>.
29. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir / ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS*. 2004;18(11):1529-1537. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15238771>.
30. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b\*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18444831>.
31. Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18256392>.
32. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18387667>.
33. The SMART/INSIGHT and the D:A:D Study Groups TSIatDADSG. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18753925>.
34. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med*. 2010;11(2):130-136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19682101>.
35. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS*. 2011;25(10):1289-1298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21516027>.
36. Durand M, Sheehy O, Baril JG, Leloir J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *Journal of Acquired Immune Deficiency Syndromes*. 2011;57(3):245-253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21499115>.
37. Palella FJ, Althoff KN, Moore R, et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD. Presented at: Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/abacavir-use-and-risk-myocardial-infarction-na-accord>.
38. Young J, Xiao Y, Moodie EE, et al. Effect of cumulating exposure to abacavir on the risk of cardiovascular disease events in patients from the Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndromes*. 2015;69(4):413-421. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25932884>.
39. Marcus JL, Neugebauer RS, Leyden WA, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. *Journal of Acquired Immune Deficiency Syndromes*. 2016;71(4):413-419. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26536316>.
40. Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med*. 2016;14:61. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27036962>.
41. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased

risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *Journal of Acquired Immune Deficiency Syndromes*. 2009;51(1):20-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19282778>.

42. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2011;53(1):84-91. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21653308>.
43. Ribaud HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis*. 2011;52(7):929-940. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21427402>.
44. Ding X, Andraca-Carrera E, Cooper C, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *Journal of Acquired Immune Deficiency Syndromes*. 2012;61(4):441-447. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22932321>.
45. Zack J, Chuck S, Chu H, et al. Bioequivalence of the rilpivirine/emtricitabine/tenofovir alafenamide single-tablet regimen. *Journal of Bioequivalence & Bioavailability*. 2016;8(2):49-54. Available at: <http://www.omicsonline.org/open-access/bioequivalence-of-the-rilpivirineemtricitabinetenofovir-alafenamidesingletablet-regimen-jbb-1000266.pdf>.
46. Casetti I, Madruga JV, Suleiman JM, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. *HIV Clinical Trials*. 2007;8(3):164-172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17621463>.
47. Molina JM, Podszadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Research and Human Retroviruses*. 2007;23(12):1505-1514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18160008>.
48. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18722869>.
49. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18614861>.
50. Smith KY, Weinberg WG, DeJesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS Res Ther*. 2008;5:5. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18373851>.
51. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19647866>.
52. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379(9835):2429-2438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748590>.
53. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379(9835):2439-2448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748591>.
54. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clinical Trials*. 2012;13(4):228-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22849964>.
55. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074642>.
56. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis*.

2003;36(8):1070-1073. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12684922>.

57. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis*. 2006;42(2):283-290. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16355343>.
58. Gervasoni C, Meraviglia P, Landonio S, et al. Low body weight in females is a risk factor for increased tenofovir exposure and drug-related adverse events. *PLoS one*. 2013;8(12):e80242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24312465>.
59. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS*. 2009;23(15):1971-1975. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19696652>.
60. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *Journal of Acquired Immune Deficiency Syndromes*. 2006;43(3):278-283. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17079992>.
61. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis*. 2008;197(1):102-108. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18171292>.
62. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clinical Pharmacology and Therapeutics*. 2008;83(2):265-272. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17597712>.
63. Gilead. Stribild package insert. 2017. Available at: [http://www.gilead.com/~media/Files/pdfs/medicines/hiv/stribild/stribild\\_pi.pdf](http://www.gilead.com/~media/Files/pdfs/medicines/hiv/stribild/stribild_pi.pdf).
64. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. 2010;51(8):963-972. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20828304>.
65. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis*. 2011;203(12):1791-1801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21606537>.
66. Perrot S, Aslangul E, Szwebel T, Caillat-Vigneron N, Le Jeune C. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*. 2009;15(2):72-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19265350>.
67. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(9):e96-138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25234519>.
68. Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *Journal of Acquired Immune Deficiency Syndromes*. 2015;70(5):515-519. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26262777>.
69. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24698485>.
70. Feinberg J, Clotet B, Khuong-Josses MA, et al. Once-daily dolutegravir (DTG) is superior to darunavir/ritonavir (DRV/r) in antiretroviral-naive adults: 48 week results from FLAMINGO (ING114915). Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy. 2013. Denver, CO.
71. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. *Journal of the International AIDS Society*. 2014;17(4 Suppl 3):19490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25393999>.
72. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus



- ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *The Lancet HIV*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28729158>.
73. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS*. 2015;29(13):1723-1725. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26372287>.
74. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS*. 2008;22(14):1890-1892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18753871>.
75. Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *The Journal of Antimicrobial Chemotherapy*. 2017;72(6):1752-1759. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28333231>.
76. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med*. 2017;18(1):56-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27860104>.
77. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. *Journal of Acquired Immune Deficiency Syndromes*. 2017;74(4):423-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27984559>.
78. Kheloufi F, Boucherie Q, Blin O, Micallef J. Neuropsychiatric events and dolutegravir in HIV patients: a worldwide issue involving a class effect. *AIDS*. 2017;31(12):1775-1777. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28700395>.
79. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2014;65(3):e118-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24256630>.
80. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *Journal of Acquired Immune Deficiency Syndromes*. 2014;65(3):e121-124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24346640>.
81. Gilead. Genvoya package insert. 2017. Available at: [http://www.gilead.com/~media/files/pdfs/medicines/hiv/genvoya/genvoya\\_pi.pdf](http://www.gilead.com/~media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf).
82. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clinical Pharmacology and Therapeutics*. 2009;85(1):64-70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18815591>.
83. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *Journal of Acquired Immune Deficiency Syndromes*. 2012;61(1):32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22732469>.
84. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: final 5-year results from STARTMRK. *Journal of Acquired Immune Deficiency Syndromes*. 2013;63(1):77-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23412015>.
85. Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. *The Lancet HIV*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28918877>.
86. Merck Sharp & Dohme Corp. Isentress package insert. 2017. Available at: [http://www.merck.com/product/usa/pi\\_circulars/i/isentress/isentress\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf). Accessed: Sep 20, 2017.
87. Gray J, Young B. Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review. *AIDS Patient Care and STDs*. 2009;23(9):689-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19663717>.
88. Snedecor SJ, Khachatryan A, Nedrow K, et al. The prevalence of transmitted resistance to first-generation non-



- nucleoside reverse transcriptase inhibitors and its potential economic impact in HIV-infected patients. *PloS one*. 2013;8(8):e72784. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23991151>.
89. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naïve HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *Journal of Acquired Immune Deficiency Syndromes*. 2012;60(1):33-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22343174>.
  90. Janssen. Edurant package insert. 2017. Available at: <http://www.edurant.com/shared/prescribing-information-edurant.pdf>. Accessed: Oct 6, 2017.
  91. Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154(7):445-456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21320923>.
  92. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naïve, HIV-1 patients in two Phase III randomized trials. *AIDS*. 2013;27(6):939-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23211772>.
  93. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. *AIDS*. 2014;28(7):989-997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24508782>.
  94. Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naïve adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24522178>.
  95. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. 2014;161(1):1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24979445>.
  96. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *Journal of the International AIDS Society*. 2014;17(4 Suppl 3):19512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25394021>.
  97. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *Journal of the International AIDS Society*. 2014;17:19214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25192857>.
  98. Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. *Medicine (Baltimore)*. 2016;95(3):e2480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26817882>.
  99. Bristol-Myers Squibb. Sustiva package insert. 2016. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020972s049-021360s0381bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020972s049-021360s0381bl.pdf). Accessed: Sep 20, 2017.
  100. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6\*6\*6 allele carriers. *J Cardiovasc Electrophysiol*. 2016;27(10):1206-1213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27333947>.
  101. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*. 2002;16(2):299-300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11807320>.
  102. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25(18):2301-2304. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21918421>.
  103. van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naïve adults: week 96 efficacy and safety from a randomized phase 3b study. *AIDS*. 2016;30(2):251-259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26684822>.
  104. Lathouwers E, De Meyer S, Dierynck I, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther*. 2011;16(1):99-108. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21311113>.

105. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naïve HIV-1 patients: the ARTEN Trial. *Antivir Ther.* 2011;16(3):339-348. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21555816>.
106. Ryom L, Lundgren JD, El-Sadr WM, et al. Association between cardiovascular disease and temporarily used protease inhibitors. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/association-between-cardiovascular-disease-temporarily-used-protease-inhibitors>.
107. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. *HIV Med.* 2013;14(1):49-59. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23088336>.
108. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. *Clin Infect Dis.* 2015;60(12):1842-1851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25767256>.
109. Gilead. Tybost package insert. 2017. Available at: [http://www.gilead.com/~media/Files/pdfs/medicines/hiv/tybost/tybost\\_pi.pdf](http://www.gilead.com/~media/Files/pdfs/medicines/hiv/tybost/tybost_pi.pdf). Accessed: Sep 20, 2017.
110. Janssen Therapeutics. Prezcoibix package insert. 2017. Available at: <https://www.prezcoibix.com/sites/www.prezcoibix.com/files/prescribing-information-prezcoibix.pdf>. Accessed: Sep 20, 2017.
111. Tashima K, Crofoot G, Tomaka FL, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. *AIDS Res Ther.* 2014;11:39. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25926858>.
112. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *Journal of Acquired Immune Deficiency Syndromes.* 2010;53(3):323-332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20032785>.
113. Smith KY, Tierney C, Mollan K, et al. Outcomes by sex following treatment initiation with atazanavir plus ritonavir or efavirenz with abacavir/lamivudine or tenofovir/emtricitabine. *Clin Infect Dis.* 2014;58(4):555-563. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24253247>.
114. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J Infect Dis.* 2013;208(1):32-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23532097>.
115. Gallant JE, Koenig E, Andrade-Villanueva JF, et al. Brief report: cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results. *Journal of Acquired Immune Deficiency Syndromes.* 2015;69(3):338-340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26181707>.
116. Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and atazanavir prescribing. *Clinical Pharmacology and Therapeutics.* 2016;99(4):363-369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26417955>.
117. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS.* 2007;21(9):1215-1218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17502736>.
118. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS.* 2011;25(13):1671-1673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21716074>.
119. Hamada Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis.* 2012;55(9):1262-1269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22820542>.
120. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis.* 2012;55(9):1270-1272. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22820540>.

121. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014;384(9958):1942-1951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25103176>.
122. Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS*. 2011;25(17):2113-2122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21857490>.
123. Bedimo RJ, Drechsler H, Jain M, et al. The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health. *PLoS one*. 2014;9(8):e106221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25170938>.
124. Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014;14(7):572-580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24783988>.
125. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *Journal of the International AIDS Society*. 2017;20(1):1-7. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28537061>.
126. Figueroa MI, Rolón MJ, Patterson P, Gun A, Cahn P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 96 week results of the PADDLE trial. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: [http://www.ias2017.org/Portals/1/Files/IAS2017\\_LO.compressed.pdf?ver=2017-07-27-211231-197](http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197).
127. Taiwo BO, Zheng L, Nyaku AN, et al. ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: [http://www.ias2017.org/Portals/1/Files/IAS2017\\_LO.compressed.pdf?ver=2017-07-27-211231-197](http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197).
128. Sued O, Figueroa MI, Gun A, et al. Dual therapy with darunavir/ritonavir plus lamivudine for HIV-1 treatment initiation: week 24 results of the randomized ANDES study. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: [http://www.ias2017.org/Portals/1/Files/IAS2017\\_LO.compressed.pdf?ver=2017-07-27-211231-197](http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197).