

## Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

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The following sections provide detailed information on antiretroviral (ARV) drugs that the Panel recommends for initial therapy for people with HIV, including the drugs' characteristics and adverse effects profiles, results from related clinical trials, and Panel recommendations on their use.

### *Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy*

**Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy–Naïve Patients**

Characteristics	ABC/3TC	3TC <sup>a</sup>	TDF/3TC	TAF/FTC	TDF/FTC
Dosing Frequency	Once daily	Once daily	Once daily	Once daily	Once daily
Available Coformulations for ART-Naïve Patients	<ul style="list-style-type: none"> <li>• ABC/3TC</li> <li>• DTG/ABC/3TC</li> </ul>	DTG/3TC	<ul style="list-style-type: none"> <li>• TDF/3TC</li> <li>• DOR/TDF/3TC</li> <li>• EFV 600 mg/TDF/3TC</li> <li>• EFV 400 mg/TDF/3TC</li> </ul>	<ul style="list-style-type: none"> <li>• TAF 25 mg/FTC</li> <li>• BIC/TAF 25 mg/FTC</li> <li>• DRV/c/TAF 10 mg/FTC</li> <li>• EVG/c/TAF 10 mg/FTC</li> <li>• RPV/TAF 25 mg/FTC</li> </ul>	<ul style="list-style-type: none"> <li>• TDF/FTC</li> <li>• EFV/TDF/FTC</li> <li>• EVG/c/TDF/FTC</li> <li>• RPV/TDF/FTC</li> </ul>
Adverse Effects	<p><b>ABC</b></p> <ul style="list-style-type: none"> <li>• HSR to ABC is associated with the presence of HLA-B*5701 allele.</li> <li>• Increase in CV events is associated with ABC use in some cohort studies.</li> </ul>	See below	<p><b>TDF</b></p> <ul style="list-style-type: none"> <li>• Renal insufficiency, proximal renal tubulopathy</li> <li>• Decrease in BMD</li> <li>• Renal and bone toxicity are exacerbated by pharmacologic boosters.</li> </ul>	<p><b>TAF</b></p> <ul style="list-style-type: none"> <li>• Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF)</li> <li>• Decrease in BMD (less than with TDF; similar to with ABC)</li> <li>• Some studies have reported greater weight gain with TAF than with TDF.</li> </ul>	<p><b>TDF</b></p> <ul style="list-style-type: none"> <li>• Renal insufficiency, proximal renal tubulopathy</li> <li>• Decrease in BMD</li> <li>• Renal and bone toxicity are exacerbated by pharmacologic boosters.</li> </ul>
	3TC: No significant adverse effects			FTC: Skin discoloration	

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

Characteristics	ABC/3TC	3TC <sup>a</sup>	TDF/3TC	TAF/FTC	TDF/FTC
Other Considerations	<b>ABC</b> <ul style="list-style-type: none"> <li>Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list.</li> </ul> <b>3TC</b> <ul style="list-style-type: none"> <li>Epivir HBV is for the treatment of HBV and contains a different dose of 3TC than the formulation for ART. Thus, Epivir HBV should not be used for HIV treatment.</li> <li>Coadministration of 3TC with sorbitol-containing drugs decreases 3TC concentration and should be avoided.</li> </ul>			FTC should not be used as sole treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.	
	3TC or ABC/3TC <b>should not be used</b> as treatment for HBV due to the development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.		<ul style="list-style-type: none"> <li>Also used for HBV treatment. Discontinuation may precipitate HBV flare.</li> <li>See <a href="#">Appendix B, Table 11</a> for dose recommendations in patients with renal insufficiency.</li> </ul>		

<sup>a</sup> 3TC is recommended for use with DTG in ART-naive persons and with DRV/r if ABC, TDF, and TAF are not optimal. Otherwise, dual-NRTI backbones are recommended.

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

## Summary

The Food and Drug Administration (FDA)-approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), abacavir (ABC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), lamivudine (3TC), and emtricitabine (FTC). Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States because of high rates of serious toxicities, including peripheral neuropathy and mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, lipoatrophy, and bone marrow suppression from ZDV use. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.<sup>1,2</sup>

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended as components of initial therapy. In addition, 3TC may be used as a single NRTI with dolutegravir (DTG), or, in select circumstances, with boosted darunavir (DRV). [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. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.<sup>3</sup> TAF is less likely to cause kidney and bone toxicities than TDF. TDF is associated with lower lipid levels than TAF. **Although there are insufficient data on teratogenicity in humans, TAF is now recommended as an alternative drug in pregnancy because of reassuring data from [The Antiretroviral Pregnancy Registry](#) that show no evidence of teratogenicity. Please refer to the [Perinatal Guidelines](#).** Safety, cost, and access are among the factors to consider when choosing

between these drugs. ABC/3TC, TDF/3TC, **TDF/FTC**, and 3TC are available as generic formulations.

## ***Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors***

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

Several randomized controlled trials in antiretroviral therapy (ART)-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug<sup>4-6</sup> (see the Integrase Strand Transfer Inhibitor-Based Regimen section).<sup>7</sup>

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each combination was used with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r). In patients with baseline HIV RNA  $\geq 100,000$  copies/mL, the time to virologic failure was significantly shorter with ABC/3TC than with TDF/FTC, regardless of whether the third active drug was EFV or ATV/r.<sup>4</sup> In the HEAT study, 688 participants received ABC/3TC or TDF/FTC with once-daily lopinavir/ritonavir. Virologic efficacy was similar in the two study arms, including in a subgroup of participants with HIV RNA  $\geq 100,000$  copies/mL.<sup>6</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 (59%) than among TDF/FTC-treated participants (71%).<sup>5</sup>

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

A single-tablet regimen (STR) of DTG/3TC has now been approved as an initial ARV regimen. Please refer to the Integrase Strand Transfer Inhibitor-Based Regimens section for a full discussion.

GEMINI 1 and GEMINI 2 were identically designed randomized, double-blind clinical trials that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and estimated glomerular filtration rate (eGFR)  $\geq 50$  mL/min.<sup>8,9</sup>

### **Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate**

Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of elvitegravir/cobicistat (EVG/c)/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with eGFR  $\geq 50$  mL/min.

- TAF/FTC was virologically noninferior to TDF/FTC at Week 48 (92% vs. 90% of participants had plasma HIV RNA <50 copies/mL, respectively),<sup>10</sup> but TAF/FTC was superior to TDF/FTC at Week 144 (84.2% vs. 80% of participants with plasma HIV RNA <50 copies/mL), largely driven by a higher rate of treatment discontinuation in the TDF arm.<sup>11</sup>
- Participants in the TAF arm had significantly smaller reductions in bone mineral density (BMD) at the spine and hip than those in the TDF arm through 144 weeks.<sup>11</sup> Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through Week 96.<sup>12</sup> Conversely, levels of fasting low-density lipoprotein (LDL)

cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at Week 96, with no change in total cholesterol to HDL ratio.<sup>13</sup>

Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC, with each combination administered with boosted DRV in ART-naive participants:

- A Phase 2 study of coformulated darunavir/cobicistat (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC in treatment-naive patients demonstrated similar virologic suppression rates in both arms (75% vs. 74%).<sup>14</sup> In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
- The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At Week 48, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.<sup>15</sup>

One analysis evaluated data from 14 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF and TAF when either drug was taken with or without pharmacokinetic (PK) boosters (RTV or COBI). No significant differences appeared between unboosted TDF and TAF in terms of virologic efficacy. TAF resulted in a clinically small but statistically significant greater virologic efficacy than TDF when used with PK boosters (94% vs. 92%;  $P = 0.0004$ ). No difference was seen in bone-related toxicities and clinical or laboratory adverse events between TAF and TDF, regardless of boosting. There was a small but statistically significant difference in higher rate of discontinuation due to renal adverse events in the boosted TDF subgroup compared with the boosted TAF subgroup.<sup>16</sup>

To assess the ability of TAF to maintain HIV and hepatitis B virus (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>17</sup> In this study, 96% of participants were on a TDF/FTC-containing regimen before the switch. Key results of the study showed the following:

- Among those who switched to EVG/c/TAF/FTC, HIV suppression was maintained in 91.7% of participants at Week 48, and 91.7% of participants had HBV DNA <29 log<sub>10</sub> IU/mL.
- Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.<sup>17</sup>

Although conducted in people without HIV for pre-exposure prophylaxis, the DISCOVER trial, with 5,387 treated participants, was the largest trial to directly compare the adverse effects of TAF/FTC with those of TDF/FTC.<sup>18</sup>

- TAF/FTC was noninferior to TDF/FTC for the primary endpoint of preventing HIV acquisition, and the groups did not differ statistically in overall, Grade 3–4, or serious adverse events, or in discontinuation due to adverse events.
- Changes in renal biomarkers and bone density significantly favored the TAF arm over TDF. One case of proximal tubular disease occurred in the TDF arm.
- LDL, HDL, and total cholesterol were significantly higher in the TAF arm than in the TDF arm, without significant difference in the total cholesterol to HDL ratio.

- Participants in the TAF arm gained 1.1 kg more than those in the TDF arm.

## ***Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy***

In alphabetical order.

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

ABC plus 3TC has been studied in combination with EFV, several protease inhibitors (PIs), and DTG in ART-naïve patients.<sup>7, 19-21</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 who are given ABC will have a related HSR.<sup>22, 23</sup> HLA-B\*5701 testing should be done if the use of ABC is being considered. A patient who tests positive for HLA-B\*5701 should not be given ABC, and ABC hypersensitivity should be noted on the 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 Data Collection on Adverse Events of Anti-HIV Drugs (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 an MI, particularly in participants with preexisting cardiac risk factors.<sup>24, 25</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>26-32</sup> Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.<sup>33-37</sup>
- An analysis of data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.<sup>38</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 STR with DTG.
- ABC and 3TC are available separately and as a coformulated tablet in generic tablet formulations.

- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in patients with renal dysfunction.

### *The Panel's Recommendations*

- ABC should be prescribed only 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 STR, the Panel classifies DTG/ABC/3TC as a Recommended Initial Regimen for Most People with HIV (AI) (see Characteristics of Integrase Strand Transfer Inhibitors for discussion regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, atazanavir/cobicistat (ATV/c), DRV/c, darunavir/ritonavir (DRV/r), or RAL is recommended only for patients with pretreatment HIV RNA levels <100,000 copies/mL. See Table 6 for more detailed recommendations on the use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

### **Emtricitabine (FTC) and lamivudine (3TC)**

FTC and 3TC generally are used interchangeably in combination with other ARVs. In a randomized open-label comparison of FTC and 3TC in 440 patients with virologic suppression on a 3TC-containing regimen and who substituted FTC 200 mg daily for 3TC 150 mg twice daily, FTC and 3TC were equivalent for virologic suppression and similar in rates of adverse events.<sup>39</sup> A meta-analysis of 12 trials found no significant difference in treatment success between 3TC and FTC.<sup>40</sup> In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI)—EFV or nevirapine (NVP)<sup>41</sup>—or with a boosted PI.<sup>42</sup> TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis. However, it is noteworthy that the participants in the NNRTI cohort who were taking 3TC generally had higher viral loads and lower CD4 T lymphocyte cell counts and were more likely to be using injection drugs at the start of the study than those taking FTC.<sup>41</sup> No difference was reported in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI.<sup>42</sup> A retrospective analysis of an Italian national database found that viral resistance was more common with TDF/3TC than with TDF/FTC, but this was not observed in clinical trials.<sup>43</sup>

### *Adverse Effects*

- Both FTC and 3TC have been well tolerated with no significant treatment-limiting adverse effects.
- In early clinical trials, FTC was infrequently associated with mild hyperpigmentation of palms and soles.

### *Other Factors and Considerations*

- 3TC is now generic in the United States and can be coformulated with other drugs, as has occurred with DOR/TDF/3TC.

- Both 3TC and FTC have activity against hepatitis B but are insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of FTC or 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- The dose of FTC or 3TC should be adjusted in patients with creatinine clearance (CrCl) <50 mL/min.
- No significant drug interactions have been identified with FTC. Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.
- Both FTC and 3TC select for the M184V mutation when viral suppression is suboptimal.

#### *The Panel's Recommendation*

- FTC and 3TC are considered interchangeable in combination with other ARV drugs (**AI**).

#### **Lamivudine (3TC) as Single NRTI**

Based on the GEMINI-1 and GEMINI-2 studies<sup>9</sup> that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naïve patients with HIV RNA <500,000 copies/mL, 3TC may be used as a single NRTI with DTG (see [Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs](#) for more information). In addition, based on the ANDES trial, if ABC, TDF, and TAF cannot be used, 3TC can also be used as a single NRTI with DRV/r.<sup>44</sup> (see Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal.)

#### *Other Factors and Considerations*

- 3TC is available as an STR with DTG.
- 3TC has activity against HBV but is insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- 3TC is available in two brand-name formulations (one for HIV and the other for HBV), but the doses are different. The dose for HIV treatment is 3TC 300 mg daily.
- The dose of 3TC should be adjusted in patients with CrCl <50 mL/min.
- Sorbitol-containing drugs can decrease 3TC concentration, and coadministration should be avoided.

#### *The Panel's Recommendations*

The Panel recommends the use of DTG/3TC (**AI**) as a *Recommended Initial Regimen for Most People with HIV* with three exceptions. DTG/3TC is **not recommended** for—

- Individuals with HIV RNA >500,000 copies/mL,
- Individuals with HBV coinfection or whose HBV status is unknown, or
- Individuals starting ART before the results of genotypic resistance testing for reverse transcriptase are available.

## Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

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

### *Adverse Effects*

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

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

#### **Lipid Effects:**

- In randomized controlled trials in ART-naive patients, in switch studies and in a large study of preexposure prophylaxis, 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 those receiving TDF. The clinical significance of this finding is not clear.<sup>10, 45, 46</sup>

#### **Weight Gain:**

- Initiation of TAF in ART-naive individuals and in people without HIV has been associated with greater weight gain than initiation of TDF<sup>47, 48</sup> and ABC.<sup>48</sup> Significant weight gain initially was reported in a cohort of patients switching from TDF- to TAF-containing regimens.<sup>49</sup> In ADVANCE, an open-label trial conducted in South Africa that compared EFV/TDF/FTC versus DTG plus TDF/FTC versus DTG plus TAF/FTC in ART-naive patients, a greater increase in body weight was reported with initiation of TAF than with TDF.<sup>47</sup> Weight gain was most pronounced in Black women (10 kg over 96 weeks). This area is under intense investigation, and the clinical significance of the effect is still uncertain. It is also unclear whether change of therapy results in reversal of weight gain.

### *Other Factors and Considerations*

- TAF/FTC is available in FDCs with bicitgravir (BIC), DRV/c, EVG/c, or rilpivirine (RPV), allowing the regimens to be administered as a single pill taken once daily with food.
- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see [Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs](#)).
- TAF-containing regimens 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. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in patients on hemodialysis with eGFR <15 mL/min.<sup>50</sup>

- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ARV regimen because these drugs have activity against both viruses (see [Hepatitis B Virus/HIV Coinfection](#)).<sup>17</sup>
- Although there are insufficient data on teratogenicity in humans, TAF is now recommended as an alternative drug in pregnancy because of reassuring data from [the Antiretroviral Pregnancy Registry](#) that show no evidence of teratogenicity.

#### *The Panel's Recommendation*

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,<sup>51</sup> and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most people with HIV when prescribed with BIC, DTG, and RAL, and as part of Recommended Regimens in Certain Clinical Situations.

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

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.<sup>52-61</sup>

#### *Adverse Effects*

##### **Renal Effects:**

- New onset or worsening renal impairment has been associated with TDF use.<sup>62, 63</sup> Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),<sup>64</sup> and preexisting renal impairment.<sup>65</sup> Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that the risk of renal dysfunction is greater 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>66</sup>
- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC than TAF/FTC with PK boosting.<sup>16</sup>

##### **Bone Effects:**

- Although initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.<sup>67, 68</sup> BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF.

- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.<sup>69</sup> Adverse bone outcomes have been found to be more likely when TDF/FTC is coadministered with PK boosters. However, a recent meta-analysis found **no difference in bone-related toxicities between TAF and TDF, regardless of boosting.**<sup>16</sup>

#### *Other Factors and Considerations*

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.
- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring). In patients who have preexisting renal insufficiency (CrCl <60 mL/min),<sup>70</sup> use of TDF generally should be avoided. If TDF is used, a dose adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 10 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HBV/HIV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ARV regimen because these drugs have activity against both viruses (see [Hepatitis B Virus/HIV Coinfection](#)).

#### *The Panel's Recommendations*

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most people with HIV when combined with DTG 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.
- When TDF is used, especially in conjunction with a PK booster, clinicians should monitor for renal and bone safety during therapy. Boosters should be avoided when possible in patients taking TDF.

## References

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