Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Tenofovir Alafenamide (TAF, Vemlidy)  (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 25 mg

Fixed-Dose Combination Tablets

- [Descovy] Emtricitabine 200 mg plus tenofovir alafenamide (TAF) 25 mg
- [Genvoya] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg
- [Odefsey] Emtricitabine 200 mg plus rilpivirine 25 mg plus TAF 25 mg
- [Biktarvy] Bictegravir 50 mg plus emtricitabine 200 mg plus TAF 25 mg

Dosing Recommendations

[Descovy] Emtricitabine plus TAF

Pediatric, Adolescent (Weighing ≥25 kg), and Adult Dose:

- Body Weight 25 to <35 kg: 1 tablet once daily in combination with other antiretroviral (ARV) agents, except for protease inhibitors (PIs) that require a CYP3A inhibitor (i.e., emtricitabine/TAF [Descovy] can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but not a boosted PI).
- Body Weight ≥35 kg: 1 tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

Pediatric, Adolescent (Weighing ≥25 kg), and Adult Dose:

- 1 tablet once daily with food in ARV-naive patients. This dose of Genvoya can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

Pediatric, Adolescent (Weighing ≥35 kg), and Adult Dose:

- 1 tablet once daily with a meal in ARV-naive patients with HIV-1 RNA ≤100,000 copies per mL. This dose of Odefsey can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA ≤100,000 copies per mL). This dose of Odefsey can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA ≤100,000 copies per mL).

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before using TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TAF is stopped.
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC (see the Emtricitabine, Elvitegravir, Cobicistat, Rilpivirine, and Bictegravir sections).
- Use of Genvoya is not FDA-recommended with other ARV drugs, but this FDC has safely been used with darunavir. Descovy can be safely used with cobicistat- or ritonavir-boosted darunavir or atazanavir in patients weighing ≥35 kg.
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs co-formulated with cobicistat.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal) because it contains rilpivirine.

Metabolism/Elimination

- TAF undergoes renal excretion.
Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Tenofovir alafenamide (TAF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. P-gp inducers are expected to decrease TAF exposure, and P-gp inhibitors are expected to increase absorption and plasma concentrations of TAF.\(^2\) Coadministration of TAF with rifamycins is not recommended.\(^3\)

- Genvoya contains elvitegravir and cobicistat in addition to TAF. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by UGT1A1/3, and by oxidative metabolism pathways. Elvitegravir is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits adenosine triphosphate-dependent transporters BCRP and P-gp and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both elvitegravir and cobicistat.

- **Absorption:** Administering elvitegravir and bictegravir concurrently with antacids lowers plasma concentrations of these antiretroviral (ARV) drugs. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. Administration of Genvoya (which contains elvitegravir) or Biktarvy (which contains bictegravir) should be separated from administration of antacids by at least 2 hours, but preferably 4 hours. Chelation by high concentrations of divalent cations, such as iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and bictegravir. Because of this, Genvoya or Biktarvy should be administered at least 4 hours before and after chelating agents.

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\(^1\) TAF 25 mg tablets (Vemlidy) are FDA-approved for treatment of HBV. In select circumstances, TAF might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

\(^2\) The TAF 25-mg tablet is not recommended for use in patients with estimated creatinine clearance (CrCl) <15 mL/min, TAF-containing co-formulations are not recommended in patients with estimated CrCl <30 mL/min.

\(^3\) TAF Dosing in Patients with Renal Insufficiency:

- The TAF 25-mg tablet is not recommended for use in patients with estimated creatinine clearance (CrCl) <15 mL/min, TAF-containing co-formulations are not recommended in patients with estimated CrCl <30 mL/min.
- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but should not be used in patients with severe hepatic impairment because they have not been studied in that group.

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before or after iron supplements or multivitamins containing iron.

- Odefsey contains rilpivirine, which is a CYP3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.

- Before Genvoya, Odefsey, Descovy, or Biktarvy is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.

- **Renal elimination:** Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of TAF or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Genvoya.

- **Protease inhibitors:** Genvoya should not be administered concurrently with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A metabolism.

### Major Toxicities

- **More common:** Nausea, diarrhea, headache.

- **Less common (more severe):** Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of nucleoside reverse transcriptase inhibitors.

### Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

### Pediatric Use

**Approval**

Descovy, a fixed-dose combination (FDC) drug that contains emtricitabine and TAF (FTC/TAF), is Food and Drug Administration (FDA)-approved for use in children aged ≥6 years and weighing ≥25 kg when used as part of an antiretroviral therapy regimen that does not include a ritonavir- or cobicistat-boosted protease inhibitor (PI). Descovy is FDA-approved for use in children aged ≥6 years and weighing ≥35 kg when used in combination with any antiretroviral (ARV) drugs, including ritonavir- or cobicistat-boosted PIs. Odefsey, an FDC containing TAF, emtricitabine, and rilpivirine (TAF/FTC/RPV), is FDA-approved for use in children weighing ≥35 kg. Genvoya, an FDC containing elvitegravir, cobicistat, emtricitabine, and TAF (EVG/COBI/FTC/TAF), is FDA-approved for use in children aged ≥6 years and weighing ≥25 kg when used as the single-tablet regimen without other ARVs (Table A). Biktarvy is only available as part of the FDC Biktarvy, which contains bictegravir, emtricitabine, and TAF (BIC/FTC/TAF). Biktarvy is not FDA-approved for use in children or adolescents, but it was reported to be safe and effective in a small study in adolescents.

TAF has antiviral activity and efficacy against hepatitis B virus (HBV). Testing for HBV should be performed prior to starting TAF treatment. If HBV is found, there could be rebound of clinical hepatitis when TAF is stopped. For more information about hepatitis rebound in patients with HBV/HIV coinfection, see the Pediatric Opportunistic Infections Guidelines. TAF alone (as Vemlidy) is FDA-approved for use in persons aged ≥8 years, and is only approved for treating HBV, not HIV.

### Formulations

TAF-containing pills are smaller than their tenofovir disoproxil fumarate (TDF)-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills. TAF is available as the coformulated tablets FTC/TAF, FTC/RPV/TAF, EVG/COBI/FTC/TAF, and BIC/FTC/TAF (Descovy, Odefsey, Genvoya, and Biktarvy, respectively). EVG/COBI/FTC/TAF (Genvoya) contains TAF 10 mg while FTC/TAF, FTC/RPV/TAF, and BIC/FTC/TAF (Descovy, Odefsey, and Biktarvy, respectively) contain TAF 25 mg. Cobicistat boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, administration of EVG/COBI/FTC/TAF (Genvoya), which contains TAF 10 mg and cobicistat, achieves TFV-DP systemic exposure that is similar to the exposure achieved by FTC/RPV/TAF (Odefsey) or BIC/FTC/TAF (Biktarvy), which contain TAF 25 mg but no cobicistat.
Both TDF and TAF are prodrugs of the nucleotide reverse transcriptase inhibitor tenofovir (TFV). After oral administration, TDF is well absorbed and is so rapidly metabolized to TFV that TDF itself cannot be measured in blood (even when plasma is sampled within 5 minutes of administration). TFV is the main compound measurable in plasma after TDF administration. From the bloodstream, TFV enters cells and is phosphorylated to the active agent TFV-DP. TAF also has good oral bioavailability. Within the enterocyte and liver, TAF is not metabolized to TFV as quickly as TDF, so the plasma TFV concentration is much lower with administration of TAF than with TDF, and the main component in plasma after TDF administration. From the bloodstream, TFV enters cells and is phosphorylated to the active agent TFV-DP.

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The key pharmacokinetic difference between TDF and TAF is that TDF results in higher plasma TFV concentrations than TAF, but when administered at FDA-approved doses, both drugs produce high and therapeutically effective intracellular TFV-DP concentrations. Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy equivalent to TDF, but should avoid the toxicities that are specifically related to plasma TFV. High plasma TFV concentration has been linked to TDF-related endocrine disruption that is associated with low bone mineral density (BMD). High plasma TFV has also been closely associated with both glomerular and proximal tubular renal toxicity.

Table B. Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV: TAF versus TDF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TAF 8 mg (N = 9)</th>
<th>TDF 300 mg (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TFV AUC&lt;sub&gt;tau&lt;/sub&gt; (ng*h/mL)</td>
<td>65.5 (23.5)</td>
<td>1,918.0 (39.4)</td>
</tr>
<tr>
<td>Plasma TFV C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>4.2 (24.7)</td>
<td>252.1 (36.6)</td>
</tr>
<tr>
<td>Plasma TFV C&lt;sub&gt;tau&lt;/sub&gt; (ng/mL)</td>
<td>2.1 (33.8)</td>
<td>38.7 (44.7)</td>
</tr>
<tr>
<td>PBMC TFV-DP AUC&lt;sub&gt;tau&lt;/sub&gt; (µM*h)</td>
<td>3.5 (77.1)</td>
<td>3.0 (119.6)</td>
</tr>
</tbody>
</table>

* Mean age 38 years; range 20–57 years

**Note:** Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C<sub>max</sub> is the maximum concentration.

**Key to Acronyms:** AUC = area under the curve; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV-DP = tenofovir diphosphate.
combination with elvitegravir, cobicistat, and emtricitabine;\textsuperscript{19,22} with emtricitabine and rilpivirine;\textsuperscript{23} with darunavir, cobicistat, and emtricitabine;\textsuperscript{24} and when TAF and emtricitabine are administered in combination with other ARV drugs.\textsuperscript{25} The combination of TAF, elvitegravir, cobicistat, and emtricitabine has been shown to have similar efficacy when used in adults and two groups of children: those aged ≥12 years and weighing ≥35 kg\textsuperscript{26} and those aged ≥6 years and weighing ≥25 kg.\textsuperscript{27}

**Pharmacokinetics**

**Drug Exposure and Virologic Response**

Virologic suppression is most closely related to intracellular TFV-DP concentrations. At clinically meaningful doses, TAF generates peripheral blood mononuclear cell TFV-DP concentrations in adults that are about sevenfold higher than those generated with TDF.\textsuperscript{13,19} Higher TFV-DP concentrations result in a stronger antiviral potency\textsuperscript{13} and a higher barrier to resistance.\textsuperscript{28,29} Therefore, compared to TDF, TAF may have a potentially enhanced ability to maintain effectiveness with nucleoside reverse transcriptase inhibitor (NRTI)-resistant virus. The mean TFV-DP concentration is higher in youths aged 12 to 18 years than in adults: 221.8 fmol/million cells (with a coefficient of variation [CV] of 94.4%) versus 120.8 fmol/million cells (CV 91.4%), respectively.\textsuperscript{26}

**Drug Exposure and Safety: All Age Groups**

FTC/TAF (Descovy) can be safely combined with dolutegravir or raltegravir without concern for drug interactions. Emtricitabine and TAF have also safely been combined with bictegravir in the fixed-dose combination Biktarvy.

When FTC/TAF (Descovy), which contains TAF 25 mg, is combined with cobicistat- or ritonavir-boosted atazanavir, darunavir, or lopinavir, the P-gp inhibitors cobicistat or ritonavir increase the TAF exposure to higher concentrations than those seen with use of EVG/COBI/FTC/TAF (Genvoya) which contains TAF 10 mg. However, the plasma TFV concentrations (the cause of bone and renal toxicity) are still much lower than those seen with the use of Stribild, an FDC that contains elvitegravir, cobicistat, emtricitabine, and TDF (see Table C).

**Table C. Plasma TAF and Plasma TFV Exposures for TAF 10 mg or TAF 25 mg Used in Combination with Boosted Protease Inhibitors**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>TAF AUC(a)</th>
<th>TAF AUC Ratio TAF Containing Regimen/ Genvoya (10 mg TAF) Adult Exposure</th>
<th>TFV AUC(a)</th>
<th>TFV AUC Ratio TFV Containing Regimen/ Stribild (300 mg TDF) Adult Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stribild (EVG/COBI/FTC/TDF 300 mg)</td>
<td>N/A</td>
<td>N/A</td>
<td>4,400</td>
<td>1.00</td>
</tr>
<tr>
<td>Genvoya (EVG/COBI/FTC/TAF 10 mg)</td>
<td>210</td>
<td>1.0</td>
<td>290</td>
<td>0.07</td>
</tr>
<tr>
<td>DRV/r plus TAF 25 mg(b)</td>
<td>196</td>
<td>0.93</td>
<td>259</td>
<td>0.06</td>
</tr>
<tr>
<td>DRV/c plus TAF 25 mg</td>
<td>239</td>
<td>1.1</td>
<td>935</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Pediatric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stribild for ages 12–18 years</td>
<td>N/A</td>
<td>N/A</td>
<td>6,028</td>
<td>1.37</td>
</tr>
<tr>
<td>Genvoya for ages 12–18 years</td>
<td>200</td>
<td>0.95</td>
<td>290</td>
<td>0.07</td>
</tr>
<tr>
<td>Genvoya for ages 6–12 years</td>
<td>330</td>
<td>1.6</td>
<td>440</td>
<td>0.10</td>
</tr>
</tbody>
</table>

\(a\) AUC: ng*h/mL

\(b\) Values for this row do not come from observed data. These values were predicted based on data from studies using TAF 10 mg. The AUC values predicted for TAF 25 mg were obtained by multiplying the TAF 10 mg AUC by 2.5 for both TAF and TFV AUC.

**Source:** Table modified from FDA Summary Review of tenofovir alafenamide, available at [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000SumR.pdf) and from the tenofovir alafenamide clinical pharmacology review, available at [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000ClinPharmR.pdf), using data from the Striibild product label (FDA 2017 August) and Genvoya product label (FDA 2017 September).

**Key to Acronyms:** AUC = area under curve; COBI = cobicistat; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir
Clinical trials in adults showing the safety of emtricitabine/TAF administered with ritonavir-boosted atazanavir or ritonavir-boosted darunavir have used emtricitabine/TAF 200 mg/10 mg, a formulation not available in the United States. The FDA states that when emtricitabine/TAF 200 mg/25 mg (Descovy) is combined with cobicistat- or ritonavir-boosted atazanavir, darunavir, or lopinavir in adults, “no clinically significant drug interactions have been observed or are expected,” so the combination of emtricitabine/TAF (Descovy) is FDA-approved for adults independent of the accompanying ARVs (which may include a boosted PI or an INSTI).

Moreover, in Trial 299-0102, a Phase 2b trial in adults comparing a regimen of darunavir/cobicistat (DRV/c) plus emtricitabine/TAF 10 mg to a regimen of DRV/c plus emtricitabine/TDF, there was a concern of worse Week 48 virologic outcome for the TAF 10 mg arm. Hence, emtricitabine/TAF 25 mg was recommended for approval instead of emtricitabine/TAF 10 mg. This is not the case in Canada or Europe, where emtricitabine is combined with TAF 10 mg in an FDC and used in combination with boosted PIs.

Drug Exposure and Safety: Aged 12 Years to 18 Years and Weighing ≥35 kg

Studies of EVG/COBI/FTC/TAF (Genvoya) in children aged 12 to 18 years and weighing ≥35 kg showed that drug exposures were similar to those found in adults (Table C), and that the drug was well tolerated and efficacious over 48 weeks of study. Since these drug exposures were similar to those seen in adults, emtricitabine/TAF was also FDA-approved for this age and weight group, independent of the accompanying ARV drugs in the regimen (which may include a boosted PI or an INSTI). The adult dose formulation of Biktarvy (which contains bictegravir 50 mg, emtricitabine 200 mg, and TAF 25 mg) was administered to youths aged 12 to <18 years and weighing ≥35 kg who had had viral loads <50 copies/mL for at least 6 months. The drug was well tolerated, and all of the 24 participants had viral loads <50 copies/mL at 24 weeks.

Drug Exposure and Safety: Aged 6 Years to <12 Years and Weighing 25 kg to <35 kg

Studies of EVG/COBI/FTC/TAF (Genvoya) in children aged 6 to <12 years and weighing ≥25 kg showed that drug exposures were somewhat higher than those found in adults (Table C), but the drug was well tolerated and efficacious over 24 weeks of study. This led to FDA approval of Genvoya for children aged ≥6 years who weigh ≥25 kg.

Because integrase inhibitors do not increase TAF concentrations, regimens of FTC/TAF 25 mg (Descovy) plus an INSTI are expected to result in safe drug exposures that are similar to those seen with the single-tablet regimen EVG/COBI/FTC/TAF 10 mg (Genvoya). This led the FDA to approve Descovy for children aged ≥6 years and weighing ≥25 kg when used in combination with other ARVs that do not include a boosted PI.

Because cobicistat- or ritonavir-boosted atazanavir, darunavir, or lopinavir increase the TAF exposure to higher concentrations than those seen with use of EVG/COBI/FTC/TAF (Genvoya), and because there are no data on this combination in children weighing <35 kg, the safety of FTC/TAF (Descovy) combined with cobicistat- or ritonavir-boosted PIs in children with body weights between 25 kg and <35 kg cannot be assured. That is why the FDA approval for Descovy in combination with boosted PIs is limited to children weighing ≥35 kg (Table A).

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF. For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had a smaller decrease in BMD at the spine (mean change −1.30% vs. −2.86%; P < 0.0001) and hip (−0.66% vs. −2.95%; P < 0.0001) at 48 weeks than those given EVC/COBI/FTC/TDF. These differences were maintained to 96 weeks.

Renal

Studies in adolescents aged 12 to 17 years and adults show that TAF is less frequently associated with glomerular and renal tubular damage than TDF. For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had a smaller mean increase in serum...
creatinine (0.08 vs. 0.12 mg/dL; \(P < 0.0001\)) than those given EVC/COBI/FTC/TDF, and a smaller percent change from baseline in urine protein to creatinine ratio (median % change -3% vs. +20%; \(P < 0.0001\)) at 48 weeks.\(^{19}\) These differences persisted to 96 weeks of follow-up.\(^{22}\) Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearance between 30 and 69 mL/min.\(^{33}\) For TAF, less intense renal safety monitoring may be needed than with TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made.

**Lipids**

In treatment-naive adults evaluated after 48 weeks of therapy, the initiation of elvitegravir/cobicistat/emtricitabine/TAF was associated with increases in serum lipids greater than those observed with the initiation of elvitegravir/cobicistat/emtricitabine/TDF, with a mean increase in total cholesterol of 31 mg/dL versus 23 mg/dL and low-density lipoprotein (LDL) cholesterol levels of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents treated with elvitegravir/cobicistat/emtricitabine/TAF, median changes from baseline to Weeks 24 and 36 were the following: fasting total cholesterol increased 26 mg/dL and 36 mg/dL, respectively; fasting direct LDL increased 10 mg/dL and 17 mg/dL, respectively; and fasting triglycerides increased 14 mg/dL and 19 mg/dL, respectively.\(^{34}\) Monitoring serum lipids while the patient is taking TAF-containing FDCs is warranted, given these data. For more information, see the Dyslipidemia section.

**References**


