



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Tenofovir Alafenamide (TAF, Genvoya) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

### Formulations

#### 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

### Dosing Recommendations

#### Combination Tablets

[Descovy] Emtricitabine 200 mg plus TAF 25 mg

#### Pediatric/Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- 1 tablet once daily

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

#### Pediatric/Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- 1 tablet once daily with food in antiretroviral (ARV) treatment-naïve patients or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA  $< 50$  copies/mL) and 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 $\geq 35$ kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no ARV treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.

### 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 use of 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.
- If using Descovy please see the [Emtricitabine](#) section of the drug appendix.
- If using Genvoya please see the [Elvitegravir](#), [Emtricitabine](#), and [Cobicistat](#) sections of the drug appendix for additional information.
- Use of Genvoya is not recommended with other ARV drugs.
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or protease inhibitors co-formulated with cobicistat.
- When using Odefsey, refer to the [Emtricitabine](#) and [Rilpivirine](#) sections of the drug appendix. Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).

### Pharmacology

- TAF undergoes renal excretion.
- **Dosing in patients with renal insufficiency:** TAF-containing formulations are not recommended in patients with estimated creatinine clearance below 30 mL per minute.

- TAF-containing formulations do not require dosage 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.

**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#))

- **Metabolism:** Genvoya contains [elvitegravir](#) and [cobicistat](#). 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-glycoprotein and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both elvitegravir and cobicistat.
- Odefsey contains [rilpivirine](#) which is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before Genvoya or Odefsey 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 tenofovir alafenamide (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):** 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 (see <https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf>) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

**Pediatric Use**

**Approval**

TAF is Food and Drug Administration (FDA)-approved for use in children aged at least 12 years and weighing at least 35 kg when used as part of the single-tablet regimen of elvitegravir/cobicistat/emtricitabine/TAF (EVG/COBI/FTC/TAF), or when used as the co-formulated TAF/FTC as part of an antiretroviral therapy regimen. While TAF/FTC/rilpivirine (RPV) is not FDA-approved for use in persons aged <18 years, each component of the regimen is approved for use in children aged at least 12 years and weighing at least 35 kg. 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 (reviewed in [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Children](#)).

**Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate**

Both tenofovir disoproxil fumarate (TDF) and TAF are prodrugs of the nucleotide reverse transcriptase

tenofovir (TFV). After oral administration TDF is well absorbed,<sup>1,2</sup> 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).<sup>3</sup> TFV is the main compound measurable in plasma after TDF administration. From the bloodstream TFV enters cells and is phosphorylated to the active agent tenofovir diphosphate (TFV-DP).

TAF<sup>4</sup> also has good oral bioavailability.<sup>5</sup> 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 compared to TDF, and the main component in plasma is the prodrug itself, TAF.<sup>6</sup> Once inside the cell, TAF is hydrolyzed to TFV,<sup>7,8</sup> and then TFV-DP is produced by the same mechanism as for TDF. Relative to TDF, TAF more effectively delivers TFV to cells throughout the body.<sup>4</sup> Therefore a lower dose of TAF results in equivalent or higher concentrations of TFV-DP inside cells compared to the much higher doses of TDF needed to attain a similar intracellular TFV-DP concentration.

The key pharmacokinetic difference between TDF and TAF is that TDF results in higher plasma TFV concentration compared to TAF, but when administered at FDA-approved doses, both result in equivalent intracellular TFV-DP concentrations.<sup>6</sup> 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 associated with TDF-related endocrine disruption that is associated with low bone mineral density (BMD)<sup>9</sup> and with both glomerular<sup>9,10</sup> and proximal tubular<sup>11</sup> toxicity. If some of the TDF-associated nephrotoxicity is from intracellular damage to mitochondria,<sup>12</sup> studies of longer duration may be needed to confirm the renal tubular safety of TAF.

**Table 1: Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV Infection<sup>a</sup>: TAF vs. TDF.<sup>6</sup>**

Parameter	TAF 8 mg (N = 9)	TDF 300 mg (N = 6)
Plasma TFV AUC <sub>tau</sub> (ng h/mL)	65.5 (23.5)	1,918.0 (39.4)
Plasma TFV C <sub>max</sub> (ng/mL)	4.2 (24.7)	252.1 (36.6)
Plasma TFV C <sub>tau</sub> (ng/mL)	2.1 (33.8)	38.7 (44.7)
PBMC TFV-DP AUC <sub>tau</sub> (microM h)	3.5 (77.1)	3.0 (119.6)

<sup>a</sup> Mean age 38 years; range 20–57 years

**Note:** Data are mean (% coefficient of variation); tau is the dosing interval (i.e., 24 hours), 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

### ***Tenofovir Alafenamide Efficacy in Clinical Trials in Adults and Adolescents***

In adults, TAF is non-inferior to TDF over 48 weeks in its ability to control viral load in combination with elvitegravir, cobicistat, and emtricitabine,<sup>13-15</sup> with darunavir/cobicistat/emtricitabine,<sup>16</sup> and when TAF-emtricitabine is administered in combination with other antiretroviral drugs.<sup>17</sup> TAF shows similar efficacy in children aged at least 12 years and weighing at least 35 kg.<sup>18</sup>

### ***Pharmacokinetics***

#### ***Relationship of Drug Exposure to Virologic Response***

Virologic success is most closely related to intracellular TFV-DP concentrations. There are no data available for intracellular TFV-DP in children or adolescents treated with TAF, but the peripheral blood mononuclear cell TFV-DP concentration in adults is similar with TDF and TAF.<sup>6,13</sup> In 24 pediatric patients aged 12 to <18 years who received EVG/COBI/FTC/TAF the plasma TAF area under the curve was decreased 23% compared to exposures achieved in treatment-naïve adults. The clinical significance of this is unclear.<sup>19</sup>

## Formulations

TAF is available as the co-formulated tablets FTC/TAF,<sup>20</sup> EVG/COBI/FTC/TAF,<sup>19</sup> and FTC/TAF/RPV.<sup>21</sup> The amount of TAF (10 mg) in EVG/COBI/FTC/TAF is lower than the amount of TAF (25 mg) in FTC/TAF or FTC/TAF/RPV because cobicistat boosts TAF blood concentrations. TAF-containing pills are smaller than their TDF-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills.

## Toxicity

### Bone

TAF less frequently causes bone toxicity compared to TDF.<sup>13-17</sup> 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 spine (mean change  $-1.30\%$  vs.  $-2.86\%$ ;  $P < 0.0001$ ) and hip ( $-0.66\%$  vs.  $-2.95\%$ ;  $P < 0.0001$ ) at 48 weeks compared to those given EVG/COBI/FTC/TDF.<sup>13</sup> These differences were maintained to 96 weeks.<sup>22</sup>

### Renal

Short-term studies in adolescents age 12 to 17 years<sup>18</sup> and 48-week studies in adults<sup>13-17</sup> show that TAF less frequently is associated with glomerular and renal tubular damage than is TDF. For example, in one study of 1733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had smaller mean increase in serum creatinine (0.08 vs. 0.12 mg/dL;  $P < 0.0001$ ) compared to those given EVG/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<sup>13</sup>, and these differences persisted to 96 weeks of follow-up.<sup>22</sup> Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearance between 30 and 69 mL/min.<sup>23</sup> 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-naïve adults evaluated after 48 weeks of therapy, the initiation of EVG/COBI/FTC/TAF is associated with increases in serum lipids greater than those observed with the initiation of EVG/COBI/FTC/TDF, with mean increase in total cholesterol of 31 mg/dL versus 23 mg/dL and low-density lipoprotein (LDL) cholesterol of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents treated with EVG/COBI/FTC/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.<sup>24</sup> Monitoring serum lipids while the patient is taking EVG/COBI/FTC/TAF seems reasonable given these data.

### Use of Tenofovir Alafenamide in Genvoya in Children Aged 6 to <12 years

Studies are ongoing of Genvoya in children aged 6 to < 12 years and body weight  $\geq 25$  kg.<sup>25</sup>

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