



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Tenofovir Alafenamide (TAF, Vemlidy) (Last updated September 12, 2019; last reviewed September 12, 2019)

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

Formulations

Tablets: 25 mg^a

Fixed-Dose Combination Tablets

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg
- [Descovy] Emtricitabine 200 mg/TAF 25 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/TAF 25 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

Dosing Recommendations

[Biktarvy] Bictegravir/Emtricitabine/TAF

Child (Weighing <25 kg) Dose:

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg. **Studies are currently being conducted to identify the appropriate dose for this age and weight group.**

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily **with or without food** in antiretroviral (ARV) therapy-naive patients. This dose of Biktarvy can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.
- See the [bictegravir section](#) for additional information.

[Descovy] Emtricitabine/TAF

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- **Body Weight 25 kg to <35 kg:** One tablet once daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e.,

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.
- The Food and Drug Administration does not recommend using Genvoya with other ARV drugs, but this FDC has safely been used with darunavir.¹ Descovy can be safely used with cobicistat-boosted or ritonavir-boosted darunavir or atazanavir in patients weighing ≥35 kg.²
- **Do not use** Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated 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.

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: One tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

[*Genvoya*] Elvitegravir/Cobicistat/Emtricitabine/TAF

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- One 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 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/Rilpivirine/TAF

Child and Adolescent (Aged ≥ 12 Years Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily with a meal in ARV-naive patients with HIV RNA $\leq 100,000$ copies/mL. This dose of *Odefsey* can also be used to replace a current, stable ARV regimen in patients who have been virologically suppressed (HIV RNA < 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*.

[*Symtuza*] Darunavir/Cobicistat/Emtricitabine/TAF

Adult (Aged ≥ 18 Years) Dose:

- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

Metabolism/Elimination

- TAF undergoes renal excretion.

TAF Dosing in Patients with Hepatic Impairment:

- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but they should not be used in patients with severe hepatic impairment because they have not been studied in that group.

TAF Dosing in Patients with Renal Impairment:

- The TAF 25-mg tablet^a **is not recommended** for use in patients with estimated creatinine clearance (CrCl) < 15 mL/min. TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl < 30 mL/min.

^a TAF 25-mg tablets (Vemlidy) are approved by the FDA 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.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- *Metabolism:* Tenofovir alafenamide (TAF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein (P-gp) and the 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 A study in 98 healthy participants without HIV measured plasma TAF and tenofovir (TFV) exposures when TAF was administered with other antiretroviral (ARV) drugs. Coadministration of TAF with rilpivirine and dolutegravir did not change either TAF or TFV exposure. Coadministration of TAF with the P-gp and BCRP inhibitor cobicistat, or coadministration with atazanavir/ritonavir or lopinavir/ritonavir, increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in unchanged TAF AUC and a doubling of TFV AUC. Coadministration of TAF with the P-gp and BCRP inducer efavirenz decreased TAF and TFV exposures.³

- Coadministration of TAF with rifamycins is not recommended.⁴
- Genvoya contains [elvitegravir](#) and [cobicistat](#) in addition to TAF. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, 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 ARV drugs. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. Chelation by high concentrations of divalent cations, such as calcium or iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and bictegravir. Because of this, Genvoya or Biktarvy should be administered at least **2** hours before **or 6 hours** after antacids and iron, calcium, aluminum, and/or magnesium-containing supplements or multivitamins. The Food and Drug Administration (FDA) product label should be consulted for exact recommendations on the timing of dosing for each drug.
- Odefsey contains [rilpivirine](#), which is a CYP3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.
- Before Genvoya, Odefsey, Descovy, Biktarvy, or Symtuza, 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 (e.g., acyclovir, ganciclovir, and high-dose nonsteroidal anti-inflammatory drugs) 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 that contain ritonavir, because cobicistat and ritonavir have similar effects 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 (NRTIs).

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 approved by the FDA for use in children aged ≥ 6 years who weigh ≥ 25 kg (but < 35 kg) when used as part of an ARV therapy regimen that does not include a ritonavir-boosted or cobicistat-boosted protease inhibitor (PI). Descovy is approved by the FDA for use in children aged ≥ 6 years who weigh ≥ 35 kg when used in combination with any ARV drugs, including ritonavir-boosted or cobicistat-boosted PIs. Odefsey, an FDC that contains

emtricitabine, rilpivirine, and TAF (FTC/RPV/TAF), is approved by the FDA for use in children who weigh ≥ 35 kg. Genvoya, an FDC that contains elvitegravir, cobicistat, emtricitabine, and TAF (EVG/COBI/FTC/TAF), is approved by the FDA for use in children aged ≥ 6 years who weigh ≥ 25 kg when used as the single-tablet regimen without other ARV drugs (see Table A). Bictegravir is only available as part of the FDC Biktarvy, which contains bictegravir, emtricitabine, and TAF (BIC/FTC/TAF). Biktarvy is not approved by the FDA for use in children or adolescents, but it has been studied in adolescents aged 12 to <18 years who weigh ≥ 35 kg⁵ and in children aged 6 to <12 years who weigh ≥ 25 kg.⁶ Symtuza, an FDC that contains darunavir, cobicistat, emtricitabine, and TAF (DRV/COBI/FTC/TAF) is approved by the FDA for use in adults.

TAF has antiviral activity and efficacy against hepatitis B virus (HBV). Testing for HBV should be performed prior to starting treatment with TAF. 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 Infection Guidelines](#). TAF alone (as Vemlidy) is approved by the FDA for use in persons aged ≥ 8 years, and it 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 (Descovy),² FTC/RPV/TAF (Odefsey),⁷ EVG/COBI/FTC/TAF (Genvoya),⁸ BIC/FTC/TAF (Biktarvy),⁹ and DRV/COBI/FTC/TAF (Symtuza). EVG/COBI/FTC/TAF contains TAF 10 mg while FTC/TAF, FTC/RPV/TAF, and BIC/FTC/TAF 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, which contains TAF 10 mg and cobicistat, achieves TFV-DP systemic exposure that is similar to the exposure achieved by FTC/RPV/TAF or BIC/FTC/TAF, which contain TAF 25 mg but no cobicistat.

Table A. Food and Drug Administration-Approved, Tenofovir Alafenamide-Containing Formulations

Drug	Contains	Dose of TAF	Minimum Age	Minimum Body Weight	Comment
Vemlidy	TAF	25 mg	18 years	N/A	Approved for HBV treatment only.
Descovy	FTC/TAF	25 mg	6 years	25 kg	Use with an INSTI or NNRTI, but not with a boosted PI.
	FTC/TAF	25 mg	6 years	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	12 years	35 kg	Not to be used with other ARV drugs.
Genvoya	EVG/COBI/FTC/TAF	10 mg	6 years	25 kg	TAF dose is lower because of the COBI boosting.
Biktarvy ^a	BIC/FTC/TAF	25 mg	18 years	N/A	Not to be used with other ARV drugs.

^a See the [bictegravir section](#) for information about the investigational use of this drug in children and adolescents aged 12 years to 18 years who weigh ≥ 35 kg.

Key to Acronyms: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide

Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate

Both TDF and TAF are prodrugs of the NRTI TFV. After oral administration, TDF is well absorbed^{10,11} 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).¹² TFV is the main compound that is measurable in plasma after TDF administration. From the bloodstream, TFV enters cells and is phosphorylated to the active agent TFV-DP.

TAF¹³ also has good oral bioavailability.¹⁴ 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 is the prodrug itself, TAF.¹⁵ Once inside the cell, TAF is hydrolyzed to TFV,^{16,17} 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.¹³ Therefore, a much lower dose of TAF results in intracellular concentrations of TFV-DP that are equivalent to or higher than the concentrations seen after TDF administration.

The key pharmacokinetic (PK) 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.^{15,18} Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy equivalent to TDF. However, the toxicities that are specifically related to plasma TFV should not occur when using TAF. High plasma TFV concentration has been linked to TDF-related endocrine disruption that is associated with low bone mineral density (BMD).¹⁹ High plasma TFV has also been closely associated with both glomerular¹⁹⁻²¹ and proximal tubular²² renal toxicity.

Table B. Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV:^a Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate^b

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

^a The mean age of participants was 38 years, with a range of 20 to 57 years.

^b Source: Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23807155>.

Note: Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C_{max} 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 = tenofovir; TFV-DP = tenofovir diphosphate

Tenofovir Alafenamide Efficacy in Clinical Trials in Adults

In adults, TAF is noninferior to TDF in its ability to control viral load over 48 to 96 weeks when used in combination with elvitegravir, cobicistat, and emtricitabine;²³⁻²⁶ with emtricitabine and rilpivirine;²⁷ with darunavir, cobicistat, and emtricitabine;²⁸⁻³⁰ and when TAF and emtricitabine are administered in combination with other ARV drugs.³¹ In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir, FTC/TAF was noninferior to a regimen of lamivudine plus abacavir plus a third ARV drug over 48 weeks. There were no differences in BMD or the frequency of renal glomerular toxicities or renal tubular toxicities between these groups, but the TAF group showed a decline in high-density lipoprotein (HDL) cholesterol levels while the abacavir group had an increase in HDL cholesterol levels (-2 mg/dL vs. +2 mg/dL, respectively; *P* = 0.0003).³² Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated, single-tablet regimen BIC/FTC/TAF.³³⁻³⁵

Tenofovir Alafenamide Efficacy in Clinical Trials in Adolescents and Children

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 kg³⁶ and those aged ≥6 years and weighing ≥25 kg.³⁷ In one study, treatment with the single-tablet regimen BIC/FTC/TAF resulted in viral load suppression in 100% of 24 children aged 12 years to <18 years.⁵

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 two-fold¹⁸ to seven-fold higher than those generated with TDF.^{15,23} Higher TFV-DP concentrations result in a stronger antiviral potency¹⁵ and a higher barrier to resistance.^{38,39} Therefore, since TAF administration leads to higher intracellular TFV-DP concentrations than TDF, TAF may be more effective against NRTI-resistant virus than TDF. The mean TFV-DP concentration is higher in youths aged 12 years 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.³⁶

Drug Exposure and Safety: All Age Groups

FTC/TAF 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 FDC Biktarvy.

When FTC/TAF, which contains TAF 25 mg, is combined with cobicistat-boosted 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, which contains TAF 10 mg. However, the plasma TFV concentrations (the cause of bone and renal toxicity) seen with the use of EVG/COBI/FTC/TAF or TAF plus DRV/r or darunavir/cobicistat (DRV/c) 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 Tenofovir Exposures for TAF 10 mg or TAF 25 mg Used in Combination with Boosted Protease Inhibitors

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

^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 that used 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 TAF](#) and from the [TAF clinical pharmacology review](#), using data from the [Stribild product label](#) and [Genvoya product label](#).

Key to Acronyms: AUC = area under the curve; COBI = cobicistat; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

The clinical trials in adults that have shown the safety of emtricitabine plus TAF administered with ritonavir-boosted atazanavir or ritonavir-boosted darunavir have used FTC/TAF 200 mg/10 mg, a formulation not available in the United States.⁴⁰ The FDA states that when FTC/TAF 200 mg/25 mg is combined with

cobicistat-boosted or ritonavir-boosted atazanavir, darunavir, or lopinavir in adults, “no clinically significant drug interactions have been observed or are expected.” The combination of FTC/TAF 200 mg/25 mg is approved by the FDA for use in adults independent of the accompanying ARV drugs (which may include a boosted PI or an INSTI).² Moreover, in Trial 299-0102, a Phase 2b trial in adults that compared a regimen of DRV/c plus FTC/TAF 10 mg to a regimen of DRV/c plus FTC/TDF, virologic outcomes at week 48 were worse for participants in the TAF 10 mg arm compared to the TDF arm.⁴¹ Hence, FTC/TAF 25 mg was recommended for approval instead of FTC/TAF 10 mg.⁴¹ This is not the case in Canada or Europe, where emtricitabine is combined with TAF 10 mg in an FDC for use in combination with boosted PIs.

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

A study of FTC/TAF in 18 children and adolescents (aged 12 years to 18 years and weighing ≥ 35 kg) was performed using FTC/TAF 200 mg/10 mg plus a boosted third ARV drug or FTC/TAF 200 mg/25 mg with an unboosted third ARV drug. The results of this study showed TAF exposures in children and adolescents that were similar to those seen in adults. TAF was well tolerated and efficacious during the 24 weeks of study. Asymptomatic Grade 3 or 4 elevations in amylase levels were noted in five of 28 participants (18%), and Grade 3 or 4 elevations in fasting low density lipoprotein (LDL) levels were noted in two of 28 participants (7%).⁴²

Studies of EVG/COBI/FTC/TAF in children aged 12 years to 18 years and weighing ≥ 35 kg showed that TAF and TFV exposures were similar to those found in adults (see Table C) and that the drug combination was well tolerated and efficacious over 48 weeks of study.³⁶ Since these TAF and TFV exposures were similar to those seen in adults, FTC/TAF 200 mg/25 mg was also approved by the FDA for use in this age and weight group, independent of the accompanying ARV drugs in the regimen (which may include a boosted PI or an INSTI).²

The adult-dose formulation of Biktarvy (which contains bictegravir 50 mg, emtricitabine 200 mg, and TAF 25 mg) was administered to youth aged 12 years to <18 years and weighing ≥ 35 kg and who had had viral loads <50 copies/mL for at least 6 months. The drug was well tolerated, and all 24 participants had viral loads <50 copies/mL at 24 weeks.⁵ While the area under the curve (AUC) and C_{\max} for bictegravir were similar in adolescents and adults, the mean bictegravir trough in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a CV of 49%); in adults, the mean bictegravir trough was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% CI, 74–100%).⁵

BIC/FTC/TAF 50 mg/200 mg/25 mg was administered to children aged 6 years to <12 years who weighed ≥ 25 kg and who had had viral loads <50 copies/mL for ≥ 6 months on their current ARV regimens. Despite a high AUC and C_{\max} , the drug combination was well tolerated, with a fall in estimated glomerular filtration rate similar to that seen in adult studies, which is related to changes in tubular secretion of creatinine and not a true change in glomerular function. All 50 participants in the study had viral loads <50 copies/mL at Week 12, and the 26 participants with data up to week 24 likewise all had viral loads <50 copies/mL.⁶

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

Studies of EVG/COBI/FTC/TAF in children aged 6 years to <12 years who weighed ≥ 25 kg showed that TAF and TFV exposures were somewhat higher than those found in adults (see Table C), but the drug combination was well tolerated and efficacious over 24 weeks of study.^{37,43} This led to FDA approval of EVG/COBI/FTC/TAF for use in children aged ≥ 6 years and weighing ≥ 25 kg.⁸

Because integrase inhibitors do not increase TAF concentrations, regimens of FTC/TAF 25 mg 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. This led the FDA to approve FTC/TAF 25 mg for use in children aged ≥ 6 years and weighing ≥ 25 kg when used in combination with other ARV drugs that do not include a boosted PI.²

Because cobicistat-boosted or ritonavir-boosted atazanavir, darunavir, or lopinavir increase TAF exposure to concentrations that are higher than those seen with use of EVG/COBI/FTC/TAF, and because there are

no data on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with cobicistat-boosted or ritonavir-boosted PIs in children weighing between 25 kg and <35 kg cannot be assured. That is why the FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing ≥ 35 kg (see Table A).²

Dosing: Crushing Emtricitabine/Tenofovir Alafenamide Tablets

There is one report of viral load suppression in a single adult patient with HIV who received crushed FTC/TAF tablets plus crushed dolutegravir tablets. The crushed tablets were mixed with water and administered via a gastrostomy tube. Each dose was followed by a can of a nutritional supplement. No PK parameters were measured.⁴⁴

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF.^{23-25,28-31,45,46} 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 EVG/COBI/FTC/TDF.²³ These differences were maintained to 96 weeks.²⁶

Renal

Studies in adolescents aged 12 years to 17 years³⁶ and adults^{23-25,28,29,31} 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 mg/dL vs. 0.12 mg/dL; $P < 0.0001$) than 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.²³ These differences persisted to 96 weeks of follow-up.²⁶ Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.⁴⁷ 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 who were evaluated after 48 weeks of therapy, the initiation of EVG/COBI/FTC/TAF was associated with increases in serum lipids greater than those observed with the initiation of EVG/COBI/FTC/TDF, with a mean increase in total cholesterol levels of 31 mg/dL versus 23 mg/dL and a mean increase in LDL cholesterol levels of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents who were treated with EVG/COBI/FTC/TAF, median changes from baseline to Weeks 24 and 36 were the following: fasting total cholesterol levels increased 26 mg/dL and 36 mg/dL, respectively; fasting direct LDL levels increased 10 mg/dL and 17 mg/dL, respectively; and fasting triglycerides increased 14 mg/dL and 19 mg/dL, respectively.⁴⁸ Similar TAF-related increases in total cholesterol levels and LDL cholesterol levels have been found when TAF is administered with other combinations of ARV drugs.²⁹ Monitoring serum lipids while the patient is taking TAF-containing FDCs is warranted, given these data. For more information, see the [Dyslipidemia section](#).

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