

Tenofovir Alafenamide (TAF, Vemlidy)

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Formulations

Tablets: 25 mg^a

Fixed-Dose Combination Tablets:

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

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for 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](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

Dosing Recommendations

[Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

Neonate or Child (Aged <2 years and Weighing <14 kg) Dose:

- No data are currently available on the appropriate dose of Biktarvy in children aged <2 years and weighing <14 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.

Child (Aged ≥2 years and Weighing 14 kg to <25 kg) Dose:

- Data are currently **limited** on the appropriate dose of Biktarvy in children weighing <25 kg. Studies are being conducted to identify the **safety and efficacy of a low-dose Biktarvy tablet** for this age and weight group. See the Biktarvy section for details. See the [Bictegravir](#) section for additional information.

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

- One tablet once daily, with or without food. **The Food and Drug Administration approved Biktarvy for use** in antiretroviral therapy-naïve patients or to replace the current antiretroviral (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 mutations associated with resistance to the individual components of Biktarvy. **Some members on**

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 initiating TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TAF.
- The Food and Drug Administration (FDA) does not recommend using Genvoya with other ARV drugs, but this FDC tablet has safely been used with darunavir (DRV).¹ Descovy can be safely used with DRV or atazanavir in patients weighing ≥35 kg.²
- **Do not use** Genvoya with elvitegravir, cobicistat (COBI), tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated with COBI.
- 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 Dosing in Patients with Hepatic Impairment:

- TAF-containing formulations do not require dose adjustment in patients with mild or

the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) would use Biktarvy in patients with prior treatment failure who have virus with the M184V mutation. 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 an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). **In this weight band** Descovy should not be used with protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., ritonavir or cobicistat).

Body Weight ≥ 35 kg:

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

[Genvoya]

Elvitegravir/Cobicistat/Emtricitabine/TAF

Child (Aged > 2 years and Weighing 14 kg to < 25 kg) Dose

- **Data are currently limited on the appropriate dose of Genvoya in children aged < 6 years and weighing 14 kg to < 25 kg. Studies are being conducted to identify the safety and efficacy of a low-dose Genvoya tablet. See [elvitegravir](#) section for details.**

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

- One tablet once daily with food in ART-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 with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

[Odefsey] Emtricitabine/Rilpivirine/TAF

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

- One tablet once daily with a meal in ART-naive

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 metabolite tenofovir (TFV) is renally excreted.
- No dose adjustment of the TAF 25-mg tablet (Vemlidy)^a is required in patients with estimated creatinine clearance (CrCl) ≥ 15 mL/min, or in patients with estimated CrCl < 15 mL/min (i.e., end stage renal disease) who are receiving chronic hemodialysis. See the Vemlidy product label for information on the use of the TAF 25 mg tablet in patients with estimated CrCl ≤ 15 mL/min.³
- TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl < 30 mL/min.

patients with HIV RNA $\leq 100,000$ copies/mL. This dose of Odefsey 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 mutations associated with resistance to the individual components of Odefsey.

[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- One tablet once daily with food in ART-naive patients. This dose of Symtuza also can 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 mutations associated with resistance to the individual components of Symtuza.

^a TAF 25-mg tablets (Vemlidy) are approved by the FDA for treatment of HBV. In certain circumstances, TAF 25 mg tablets (Vemlidy) 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 (RPV) and dolutegravir (DTG) did not change either TAF or TFV exposure. Coadministration of TAF with the P-gp and BCRP inhibitor cobicistat (COBI), or coadministration with atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r), increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in unchanged TAF area under the curve (AUC) and a doubling of TFV AUC. Coadministration of TAF with the P-gp and BCRP inducer efavirenz decreased TAF and TFV exposures.⁴
- Coadministration of TAF with rifamycins (rifabutin, rifampin, or rifapentine) **is not recommended**.^{3,5}
- Genvoya contains [elvitegravir](#) (EVG) and [COBI](#) in addition to TAF. EVG is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative metabolism pathways. EVG is a modest inducer of CYP2C9. COBI is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, COBI inhibits the 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 EVG and COBI.
- *Absorption:* Administering EVG and bicitegravir (BIC) concurrently with antacids **or supplements that contain iron, calcium, aluminum and/or magnesium** lowers plasma concentrations of these ARV drugs. **See EVG and BIC sections for details.**
- Odefsey contains RPV, 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, high-dose nonsteroidal anti-inflammatory drugs) could reduce clearance of the TAF metabolite or emtricitabine (FTC). 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 (RTV), because COBI and RTV have similar effects on CYP3A metabolism.

Major Toxicities

- *More common:* Nausea, diarrhea, headache. In studies in adults, greater [weight gain](#) has been reported with the use of TAF than with TDF.⁶⁻ⁱⁱ
- *Less common (more severe):* Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the 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

TAF is available as a component of several fixed-dose combination (FDC) tablets. These FDC tablets are listed in [Appendix A, Table 1](#) and [Table 2](#).

Descovy, an FDC tablet that contains FTC 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 regimen that does not include a 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 RTV-boosted or COBI-boosted PIs. Odefsey, an FDC tablet that contains FTC, RPV, and TAF (FTC/RPV/TAF), is approved by the FDA¹² for use in children who weigh ≥ 35 kg. Genvoya, an FDC tablet that contains EVG, COBI, FTC, and TAF (EVG/c/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 (STR) without other ARV drugs (see Table A).¹³ BIC is available only as part of the FDC tablet Biktarvy, which contains BIC, FTC, and TAF (BIC/FTC/TAF). Biktarvy is approved by the FDA^{14,15} for use in children or adolescents who weigh ≥ 25 kg. Symtuza, an FDC tablet that contains DRV, COBI, FTC, and TAF (DRV/c/FTC/TAF) is approved by the FDA¹⁶ for use in children and adolescents who weigh ≥ 40 kg.

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, rebound of clinical hepatitis could occur when TAF is stopped. For more information about hepatitis rebound in patients with HBV/HIV coinfection, see the Pediatric Opportunistic Infection Guidelines, [Hepatitis B virus](#) section. TAF alone (as Vemlidy) is approved by the FDA for use in persons aged ≥ 8 years, but it is approved only for treating HBV, not HIV.

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	N/A	25 kg	Use with an INSTI or NNRTI, but not with a boosted PI.
	FTC/TAF	25 mg	N/A	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	12 years	35 kg	Generally not to be used with other ARV drugs. ^a
Genvoya	EVG/c/FTC/TAF	10 mg	N/A	25 kg	TAF dose is lower because of the COBI boosting. Generally not to be used with other ARV drugs. ^a
Biktarvy	BIC/FTC/TAF	25 mg	N/A	25 kg	Generally not to be used with other ARV drugs. ^a

^a Consult a specialist in HIV care before using these FDC tablets with other ARV agents.

Key: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; 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

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 (see [Appendix A, Table 2](#)). EVG/c/FTC/TAF contains TAF 10 mg while FTC/TAF, FTC/RPV/TAF, and BIC/FTC/TAF contain TAF 25 mg. COBI boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, administration of EVG/c/FTC/TAF, which contains TAF 10 mg and COBI, 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 COBI.

Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate

Both TDF and TAF are prodrugs of the NRTI TFV. After oral administration, TDF is well absorbed^{17,18} 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).¹⁹ 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.

TAF²⁰ also has good oral bioavailability.²¹ 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.²² Once inside the cell, TAF is hydrolyzed to TFV,^{23,24} 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.²⁰ 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.

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

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)

Note: The mean age of participants was 38 years, with a range of 20 to 57 years. Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C_{max} is the maximum concentration.

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>.

Key: AUC = area under the curve; AUC_{tau} = AUC for dosing interval; C_{max} = peak concentration; C_{tau} = concentration at the end of a dosing interval; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

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.^{22,25} Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy that is equivalent to the antiviral efficacy of TDF. However, the toxicities that are specifically related to high plasma TFV concentrations 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).²⁶ High plasma TFV concentration also has been closely associated with both glomerular^{26–28} and proximal tubular²⁹ renal toxicity.

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 EVG, COBI, and FTC;^{30–33} with FTC and RPV;³⁴ with DRV, COBI, and FTC;^{35–37} and when TAF and FTC are administered in combination with other ARV drugs.³⁸ In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir (ABC), FTC/TAF was noninferior to a regimen of lamivudine plus ABC plus a third ARV drug over 48 weeks. No differences occurred 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, whereas the ABC group had an increase in HDL cholesterol levels (–2 mg/dL vs. +2 mg/dL, respectively; *P* = 0.0003).³⁹ Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated STR BIC/FTC/TAF.^{40–42}

Tenofovir Alafenamide Efficacy in Clinical Trials in Adolescents and Children

The combination of TAF, EVG, COBI, and FTC has been shown to have similar efficacy when used in adults and two groups of children: those weighing ≥35 kg and aged ≥12 years⁴³ and those weighing ≥25 kg and aged ≥6 years.⁴⁴ In one study, treatment with the STR BIC/FTC/TAF resulted in viral load suppression in 100% of 24 children aged 12 years to <18 years.¹⁴

Pharmacokinetics

Drug Exposure and Virologic Response

Virologic suppression in people who are taking TAF or TDF 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 twofold²⁵ to sevenfold higher than those generated with TDF.^{22,30} Higher TFV-DP concentrations result in a stronger antiviral potency²² and a higher barrier to resistance.^{45,46} Therefore, because 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 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.⁴³

Drug Exposure and Safety: All Age Groups

FTC/TAF can be safely combined with DTG or raltegravir without concern for drug interactions. FTC and TAF also have safely been combined with BIC in the FDC tablet Biktarvy.

When FTC/TAF, which contains TAF 25 mg, is combined with boosted ATV, DRV, or LPV, the P-gp inhibitors COBI or RTV increase the TAF exposure to higher concentrations than those seen with use of EVG/c/FTC/TAF, which contains TAF 10 mg. However, the plasma TFV concentrations seen with the use of EVG/c/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 tablet that contains EVG, COBI, FTC, and TDF (see Table C).

Table C. Plasma Tenofovir Alafenamide and Plasma Tenofovir Exposures When Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate are Used with Boosted Antiretroviral Drugs

Regimen	TAF AUC ^a	TAF AUC Ratio TAF AUC of TAF-Containing Regimen/TAF AUC of Genvoya (Adult Exposure)	TFV AUC ^a	TFV AUC Ratio TFV AUC of TAF-Containing Regimen/TFV AUC of Stribild (Adult Exposure)
Adult				
Stribild (EVG/c/FTC/TDF 300 mg)	N/A	N/A	4,400	1.00
Genvoya (EVG/c/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/c/FTC/TDF 300 mg) for ages 12–18 years	N/A	N/A	6,028	1.37
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 12–18 years	200	0.95	290	0.07
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 6–12 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: AUC = area under the curve; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

The clinical trials in adults that have shown the safety of FTC plus TAF administered with ATV/r or DRV/r have used FTC/TAF 200 mg/10 mg, a formulation that is not available in the United States.⁴⁷ The FDA states that when FTC/TAF 200 mg/25 mg is combined with boosted ATV, DRV, or LPV in adults, “no clinically significant drug interactions have been observed or are expected.”² 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 than in the TDF arm.⁴⁸ Hence, FTC/TAF 25 mg was recommended for approval instead of FTC/TAF 10 mg.⁴⁸ This is not the case in Canada or Europe, where FTC is combined with TAF 10 mg in an FDC for use in combination with boosted PIs.

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

A study of FTC/TAF in 18 children and adolescents (aged 12 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 like 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%).⁴⁹

Studies of EVG/c/FTC/TAF in children aged 12 to 18 years and weighing ≥ 35 kg showed that TAF and TFV exposures were like those found in adults (see Table C) and that the drug combination was well tolerated and efficacious over 48 weeks of study.⁴³ 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 BIC 50 mg/FTC 200 mg/TAF 25 mg) was administered to youth aged 12 years 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 24 participants had viral loads <50 copies/mL at 24 weeks.¹⁴ Although the AUC and peak concentration (C_{max}) for BIC were similar in adolescents and adults, the mean BIC trough concentration in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a CV of 49%); in adults, the mean BIC trough concentration was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% confidence interval, 74% to 100%).¹⁴

BIC 50 mg/FTC 200 mg/TAF 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 (eGFR) 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.⁵⁰

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

Studies of EVG/c/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.^{44,51} This led to FDA approval of EVG/c/FTC/TAF for use in children aged ≥ 6 years and weighing ≥ 25 kg.¹³ Follow-up to 96 weeks in a small number of participants showed no change from baseline in the median spine BMD z-score, but there was a decline in the median total body BMD z-score and a possible decline in median eGFR.⁵²

Because INSTIs do not increase TAF concentrations, regimens that include FTC/TAF 25 mg plus an INSTI are expected to result in safe drug exposures that are like those seen with the STR EVG/c/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 boosted ATV, DRV, or LPV increase TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF, and because no data exist on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with COBI-boosted or RTV-boosted PIs in children weighing between 25 kg and <35 kg cannot be assured. Therefore, 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

Viral load suppression was reported in a single adult patient with HIV who received crushed FTC/TAF tablets plus crushed DTG 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.⁵³ In adults without HIV, the PKs of crushed DRV/c/FTC/TAF tablets showed decreased TAF bioavailability compared to whole tablets. The clinical implications of these findings are unclear.⁵⁴

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF.^{30–32,35–38,55,56} For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/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/c/FTC/TDF.³⁰ These differences were maintained to 96 weeks.³³ The clinical importance of these changes in BMD are unclear.

Renal

Studies in adolescents aged 12 to 17 years⁴³ and adults^{30–32,35,36,38} show that TAF is less frequently associated with glomerular and renal tubular damage than TDF.⁵⁷ For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/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 EVC/c/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.³⁰ These differences persisted to 96 weeks of follow-up.³³ Safety of EVG/c/FTC/TAF has been demonstrated in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.⁵⁸ TAF may require less intense renal safety monitoring than 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, initiation of EVG/c/FTC/TAF was associated with increases in serum lipids that were greater than those observed with the initiation of EVG/c/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/c/FTC/TAF, the following median changes from baseline occurred at Weeks 24 and 36: 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.⁵⁹ 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.³⁶ Monitoring serum lipids while the patient is taking TAF-containing FDC tablets is warranted, given these data. For more information, see [Table 15b—Dyslipidemia](#).

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