Tenofovir Alafenamide (TAF, Vemlidy)

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Formulations

Tablet: 25 mg[a]

Fixed-Dose (FDC) Combination Tablets

- [Biktarvy]
  - Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg
- [Descovy]
  - Emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Emtricitabine 120 mg/tenofovir alafenamide 15 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 FDC tablets, refer to other sections of Appendix A. Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Biktarvy] Bictegravir (BIC)/Emtricitabine (FTC)/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), Adolescent, and Adult Dose

- One tablet once daily, with or without food.

Body Weight	Dose
≥14 kg to <25 kg	BIC 30 mg/FTC 120 mg/TAF 15 mg
≥25 kg	BIC 50 mg/FTC 200 mg/TAF 25 mg

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 FDA does not recommend using Genvoya with other ARV drugs, but this FDC tablet has been safely used with DRV.[1] Descovy can be safely used[2] with DRV or atazanavir in patients weighing ≥35 kg.
- **Do not use** Genvoya with EVG, COBI, tenofovir disoproxil fumarate, FTC, lamivudine, or PIs that are coformulated with COBI.

- The U.S. Food and Drug Administration (FDA) approved Biktarvy for use in people who have no antiretroviral treatment (ART) history; in people with an ART history who are not virologically suppressed, with no known or suspected substitutions associated with resistance to the integrase strand transfer inhibitor (INSTI) class, emtricitabine, or tenofovir; or to replace the current antiretroviral (ARV) regimen in people who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no known or suspected substitutions associated with resistance to bictegravir or tenofovir. Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommend the use of Biktarvy in patients with prior treatment failure who have the virus with the M184V mutation. See the Bictegravir section for additional information.

[Descovy] FTC/TAF

Child, Adolescent, and Adult Dose

- One tablet once daily, with or without food.

Body Weight	Dose
≥14 kg to <25 kg	FTC 120 mg/TAF 15 mg, in combination with an 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 (CYP) 3A inhibitor (i.e., ritonavir [RTV] or cobicistat [COBI]).
≥25 kg to <35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI or an NNRTI. In this weight band, Descovy should not be used with PIs that require a CYP3A inhibitor (i.e., RTV or COBI).
≥35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI, NNRTI, or boosted PI.

[Genvoya] Elvitegravir (EVG)/COBI/FTC/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 ≥2 years to <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 the Elvitegravir section for details.
- 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 RPV.

Metabolism/Elimination

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 metabolite tenofovir 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[3] for information on the use of the TAF 25-mg tablet in patients with estimated CrCl ≤15 mL/min.
- TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl <30 mL/min.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose • One tablet once daily with food in ART-naive patients. This dose of Genvoya 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 Genvoya. **[Odefsey] FTC/Rilpivirine (RPV)/TAF** *Child and Adolescent (Weighing ≥25 kg) and Adult Dose* • One tablet once daily with a meal in ART-naive patients with HIV RNA ≤100,000 copies/mL. This dose of Odefsey 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 Odefsey. **[Symtuza] Darunavir (DRV)/COBI/FTC/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

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the 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 of 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, increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in

unchanged TAF area under the curve (AUC) and doubled 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 (see the Elvitegravir and Cobicistat sections for details). EVG is metabolized predominantly by cytochrome P450 (CYP) 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 OATP1B1 and OATP1B3. Potential exists for multiple drug interactions when using both EVG and COBI.
- *Absorption:* Administering EVG and bictegravir (BIC) concurrently with antacids or supplements that contain iron, calcium, aluminum and/or magnesium lowers plasma concentrations of these ARV drugs (see the Elvitegravir and Bictegravir 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 TFV 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. Greater weight gain has been reported with the use of TAF than with tenofovir disoproxil fumarate (TDF) in adults and children[6] (see Table 17h. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain for details).
- *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 maintains a list of updated HIV drug 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. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class, and Appendix A, Table 2. Antiretroviral Fixed-

Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

Descovy, an FDC tablet that contains FTC and TAF (FTC/TAF), is approved by the U.S. Food and Drug Administration (FDA) for use in children who weigh ≥14 kg to <25 kg at a dose of FTC 120 mg/TAF 15 mg and for children who weigh ≥25 kg to <35 kg at a dose of FTC 200 mg/TAF 25 mg 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 who weigh ≥35 kg at a dose of FTC 200 mg/TAF 25 mg when used in combination with any ARV drugs, including RTV-boosted or COBI-boosted PIs. Odefsey, an FDC tablet that contains FTC 200 mg, RPV 25 mg, and TAF 25 mg (FTC/RPV/TAF), is approved by the FDA[7] for use in children who weigh ≥25 kg. Genvoya, an FDC tablet that contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (elvitegravir/cobicistat [EVG/c]/FTC/TAF), is approved by the FDA for use in children who weigh ≥25 kg when used without other ARV drugs[8] (see Table A below). 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[8,9] for use in children or adolescents with body weight ≥14 kg to <25 kg at a dose of BIC 30 mg/FTC 120 mg/TAF 15 mg and for children, adolescents, and adults with body weight ≥25 kg at a dose of BIC 50 mg/FTC 200 mg/TAF 25 mg.[8,10-13] Symtuza, an FDC tablet that contains DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (darunavir/cobicistat [DRV/c]/FTC/TAF) is approved by the FDA[8] 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 Hepatitis B Virus Infection section of the Pediatric Opportunistic Infection Guidelines. TAF alone (as Vemlidy) is approved by the FDA for use in people aged ≥8 years, but it is approved only for treating HBV, not HIV.

Formulations

TAF-containing pills are smaller than their TDF-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills (see Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents). FTC/TAF available formulations contain either TAF 15 mg (for children weighing 14 to <25 kg) or TAF 25 mg (for weight ≥25 kg), but neither formulation should be used in children weighing <35 kg in combination with PIs that require boosting with RTV or COBI. Both EVG/c/FTC/TAF and DRV/c/FTC/TAF contain TAF 10 mg, whereas FTC/RPV/TAF contains TAF 25 mg. BIC/FTC/TAF is available in two strengths: one containing TAF 15 mg for children aged ≥2 years and weighing <25 kg and the other containing TAF 25 mg for people weighing ≥25 kg. COBI boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, in people weighing ≥25 kg, 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 containing TAF 25 mg but no COBI.

Table A. U.S. Food and Drug Administration–Approved Tenofovir Alafenamide-Containing Formulations

Drug	Contains	Dose of TAF	Minimum Age	Minimum Body Weight or Weight Range	Comment
Vemlidy	TAF	25 mg	6 years	≥25 kg	Approved for HBV treatment only.
Descovy	FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	Use with an INSTI or NNRTI, but **not** with a boosted PI.
	FTC/TAF	25 mg	N/A	≥25 kg	
	FTC/TAF	25 mg	N/A	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	N/A	25 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 due to the COBI boosting. **Generally not to be used with other ARV drugs.**[a]
Symtuza	DRV/c/FTC/TAF	10 mg	N/A	40 kg	TAF dose is lower due to the COBI boosting. **Generally not to be used with other ARV drugs.**[a]
Biktarvy	BIC/FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	**Generally not to be used with other ARV drugs.**[a]
	BIC/FTC/TAF	25 mg	N/A	≥25 kg	

[a] Consult a specialist in HIV care before using these fixed-dose combination tablets with other ARV agents.

Key: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; 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[11,12] 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).[13] 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.

TAF also has good oral bioavailability.[14,15] 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.[16] Once inside the cell, TAF is hydrolyzed to TFV,[17,18] 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.[14] Therefore, a much lower dose of TAF results in intracellular concentrations of TFV-DP that are higher than the

concentrations seen after TDF administration (see Table B below). In a combined analysis of two randomized crossover directly observed therapy studies of FTC/TAF (200 mg/25 mg) versus FTC/TDF (200 mg/300 mg) in adults without HIV, FTC/TAF produced 6.7- to 7.3-fold higher TFV-DP in peripheral blood mononuclear cells (PBMCs) compared to FTC/TDF across adherence levels (33%, 67%, or 100%). Additionally, the half-life of TFV-DP in PBMCs appeared numerically but not significantly longer for TAF (2.9 days; 95% confidence interval [CI], 1.5–5.5) than for TDF (2.1 days; 95% CI, 1.5–2.9). These data support a conclusion of increased potency and pharmacological forgiveness with FTC/TAF over FTC/TDF in the PBMC compartment.[19]

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, therapeutically effective intracellular TFV-DP concentrations.[16,20] 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).[21] High plasma TFV concentration also has been closely associated with both glomerular[21-23] and proximal tubular[24] renal toxicity.

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

Parameter	TAF 25 mg (n = 8)	TDF 300 mg (n = 6)
Plasma TFV AUC_{tau} (ng·h/mL)	267.7 (26.7)	1,918.0 (39.4)
Plasma TFV C_{max} (ng/mL)	15.7 (22.1)	252.1 (36.6)
Plasma TFV C_{tau} (ng/mL)	9.2 (26.1)	38.7 (44.7)
PBMC TFV-DP AUC_{tau} (μM·h)	21.4 (76.9)	3.0 (119.6)

Note: The mean age of participants was 38 years, with a range of 20 to 57 years. Data presented are mean (% coefficient of variation).

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: https://pubmed.ncbi.nlm.nih.gov/23807155.

Key: AUC_{tau} = area under the curve for the dosing interval (i.e., 24 hours); C_{max} = peak concentration; C_{tau} = concentration at the end of a dosing interval (i.e., at 24 hours, the trough concentration); 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 non-inferior to TDF in its ability to control viral load over 48 to 96 weeks when used in combination with EVG, COBI, and FTC[25-28]; with FTC and RPV[29]; with DRV, COBI, and FTC[30-32]; and when TAF and FTC are administered in combination with other ARV drugs.[33] In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir (ABC), FTC/TAF was non-inferior 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[34] (−2 mg/dL vs. +2 mg/dL, respectively; *P* = 0.0003). Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated BIC/FTC/TAF.[35-37]

Tenofovir Alafenamide Efficacy and Effectiveness in Adolescents and Children

The combination of EVG, COBI, FTC, and TAF has been shown to have similar efficacy when used in adults and two groups of children: those weighing ≥35 kg and aged ≥12 years[38] and those weighing ≥25 kg and aged ≥6 years[39] (see the Elvitegravir section for details). In a switch study, treatment with BIC/FTC/TAF resulted in viral load suppression at 48 weeks in 49 of 50 (98%) children aged 6 years to <12 years and in 50 of 50 (100%) children aged 12 years to <18 years[9] (see the Bictegravir section for details). Initial evidence in a systematic review suggests good viral suppression and no obvious safety concerns in children and adolescents on TAF-containing regimens for more than 24 to 48 weeks.[40] However, in a retrospective single-center study in France including 74 pediatric patients who received BIC/FTC/TAF for ≥6 months between 2019 and 2023, virologic failure occurred in 28 children (38%), more frequently in those with viral failure than viral suppression at baseline (68% vs. 26%); notably, only one patient developed a treatment-emergent mutation (T69D/N), which is selected by NRTIs.[41]

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. In adults, TAF generates peripheral blood mononuclear cell TFV-DP concentrations that are twofold[20] to sevenfold higher than those generated with TDF at clinically meaningful doses.[16,19,25] Higher TFV-DP concentrations result in a stronger antiviral potency[16] and a higher barrier to resistance.[42,43] 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 youth 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.[38]

Drug Exposure and Safety: All Age Groups

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

Table C. Changes in Tenofovir Alafenamide Pharmacokinetic Parameters in the Presence of Co-administered Antiretroviral Drugs in Adult Healthy Volunteers

Co-administered ARV	Dosage (Once Daily) (mg)	TAF Dosage (Once Daily) (mg)	N	Mean Ratio of TAF C_{max} (90% CI)[a]	Mean Ratio of TAF AUC (90% CI)[a]
Atazanavir	300 (+100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)
Darunavir	800 (+150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)
	800 (+100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)
Efavirenz	600	40[b]	11	0.78 (0.58, 1.05)	0.86 (0.72, 1.02)
Lopinavir	800 (+200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)

[a] Ratio represents concentrations of TAF plus the concomitant drug(s) divided by concentrations of TAF alone.

[b] Study was conducted with Descovy (FTC/TAF).

Source: Table was modified from the U.S. Food and Drug Administration Descovy product label.

Key: ARV = antiretroviral drug; AUC = area under the curve; CI = confidence interval; C_{max} = maximum concentration; FTC = emtricitabine; TAF = tenofovir alafenamide

When FTC/TAF, which contains TAF 25 mg, is combined with boosted atazanavir (ATV), DRV, or lopinavir (LPV), the P-gp inhibitors COBI or RTV increase the TAF exposure to higher concentrations than those seen with the 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 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 D below).

Table D. Plasma Tenofovir Alafenamide and Plasma Tenofovir Exposures When Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate Are Used With Boosted Antiretroviral Drugs

Regimen	**TAF AUC** (ng·h/mL)	**TAF AUC Ratio** TAF AUC of TAF-Containing Regimen/TAF AUC of Genvoya (Adult Exposure)	**TFV AUC** (ng·h/mL)	**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[a]	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] 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 U.S. Food and Drug Administration 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/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

In the CHAPAS-4 trial of African children taking TAF/FTC with DTG or a boosted PI, TAF exposures were acceptable when given with DTG, DRV/r, and lopinavir/ritonavir (LPV/r). TAF exposures were higher when TAF was given with ATV/r, but TFV exposures were comparable to administration with other boosted PIs (see Table E below).[44]

Table E. Plasma Tenofovir Alafenamide and Plasma Tenofovir Exposures When Tenofovir Alafenamide and Emtricitabine Are Administered With Dolutegravir or Boosted Protease Inhibitors

Pharmacokinetic Parameter	TAF/FTC + DTG	TAF/FTC + ATV/r	TAF/FTC + DRV/r	TAF/FTC + LPV/r	Adult Reference Using TAF 25 mg Unboosted or TAF 10 mg Boosted	Adult Reference Using TAF 25 mg With DRV/c
TAF						
AUC_{last} (ng·h/mL)	285 (79)	538 (54)	232 (61)	212 (98)	206 (72)	222
C_{max} (ng/mL)	145 (91)	309 (78)	155 (104)	155 (107)	162 (51)	181
TFV						
AUC_{tau} (ng·h/mL)	324 (29)	847 (37)	744 (26)	864 (46)	293 (27)	937
C_{max} (ng/mL)	19.6 (26)	53.2 (42)	44.5 (26)	50.3 (43)	15.2 (26)	56
C_{trough} (ng/mL)	11.0 (35)	28.1 (39)	26.1 (28)	31.2 (48)	11 (28.5)	33.2

Note: Data presented are geometric mean (% coefficient of variation).

Source: Waalewijn H, Szubert AJ, Wasmann RE, et al. First pharmacokinetic data of tenofovir alafenamide fumarate and tenofovir with dolutegravir or boosted protease inhibitors in African children: a substudy of the CHAPAS-4 trial. *Clin Infect Dis*. 2023;77(6):875-882.

Key: ATV/r = atazanavir/ritonavir; AUClast = area under the concentration-time curve from dosing to the time of the last measured concentration; AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum plasma concentration; C_{trough} = trough concentration; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; TAF = tenofovir alafenamide; TFV = tenofovir

TAF is available in FDA-approved adult FDC tablets at dosages of either 10 mg or 25 mg. The initial clinical trials in adults showing the safety of FTC/TAF with ATV/r or DRV/r used FTC 200 mg/TAF 10 mg.[45] However, in Trial GS-US-299-0102 (NCT01565850), 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.[46] Hence, FTC/TAF 25 mg was initially recommended for approval instead of FTC/TAF 10 mg.[46] The FDA label states that when FTC 200 mg/TAF 25 mg is combined with boosted ATV, DRV, or LPV in adults, "no clinically significant drug interactions have been either observed or are expected."[2] The combination of FTC 200 mg/TAF 25 mg was approved by the FDA for use in adults, independent of the accompanying ARV drugs (which may include a boosted PI or an integrase strand transfer inhibitor [INSTI]),[2] but some FDC tablets for adults (i.e., EVG/c/FTC/TAF and DRV/c/FTC/TAF) have subsequently been FDA approved with a 10-mg TAF component.[47,48]

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

A study of FTC/TAF in 18 children and adolescents (aged 12–18 years and weighing ≥35 kg) was performed using FTC 200 mg/TAF 10 mg plus a boosted third ARV drug or FTC 200 mg/TAF 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 5 of 28 participants (18%), and Grade 3 or 4 elevations in fasting low-density-lipoprotein (LDL) levels were noted in 2 of 28 participants (7%).[49]

Studies of EVG/c/FTC/TAF in children aged 12 years to 18 years and weighing ≥35 kg showed that TAF and TFV exposures were like those found in adults (see Table D above), and that the drug combination was well tolerated and efficacious over 48 weeks of study.[38] Because these TAF and TFV exposures were similar to those seen in adults, FTC 200 mg/TAF 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 formulation of Biktarvy, which contains BIC 50 mg/FTC 200 mg/TAF 25 mg, was administered to 50 children aged 6 years to <12 years and weighing ≥25 kg and 50 children and adolescents 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. All 50 participants in the study[9] had viral loads <50 copies/mL at Week 24, and 49 participants had viral loads <50 copies/mL at Week 48 (see the Bictegravir section for details).

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 D above), but the drug combination was well tolerated and efficacious over 24 weeks of study.[39,50] This led to FDA approval of EVG/c/FTC/TAF for use in children aged ≥6 years and weighing ≥25 kg.[47] 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 the median estimated glomerular filtration rate.[51]

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 coformulated 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 safety and PK studies are ongoing on the use of these combinations 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.[52] Therefore, FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing ≥35 kg (see Table A above).[2]

Drug Exposure and Safety: Aged ≥2 Years and Weighing ≥14 kg to <25 kg

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF 15 mg were administered to children aged ≥2 years weighing 14 kg to <25 kg and who had viral loads <50 copies/mL on stable antiretroviral therapy (ART). TAF exposures (ratios relative to reference, area under the concentration-time curve over the dosing interval [AUC_{tau}] 145%, area under the concentration-time curve from dosing to the time of the last measured concentration [AUC_{last}] 145%, and maximum plasma concentration [C_{max}] 173%) were generally higher than reference values derived population PK modeling based on adult

Phase 3 studies, but TFV AUC and concentrations at the end of the dosing interval (ratios relative to reference, AUC_{tau} 112%, C_{max} 143%, and concentration at the end of a dosing interval [C_{tau}] 96%) were more similar to reference values. No participants experienced any severe (Grade 3 or higher) or serious adverse events, and all drug-related adverse events were mild (Grade 1) or moderate (Grade 2). The median change in CD4 T lymphocyte (CD4) cell count was −123 cells/mm^3 at 48 weeks and −137 cells/mm^3 at 96 weeks, and the median change in CD4 percentage was +1.1% at 48 weeks and −0.8% at 96 weeks. HIV RNA at <50 copies/mL was maintained in 20 of 22 (91%) participants at 24 weeks and 21 of 22 (95%) participants at 48 weeks; when excluding missing values from the FDA snapshot algorithm, 100% of participants had HIV RNA <50 copies/mL at Weeks 24, 48, and 96 [53,54] (see the Bictegravir section for details). Safety and PK studies in children using TAF and FTC with atazanavir/cobicistat or DRV/c are ongoing.[52]

Dosing: Crushing, Splitting, and Swallowability of Emtricitabine/Tenofovir Alafenamide Tablets

Viral load suppression was reported in one 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.[55] 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.[56] Case reports in adults with HIV who are receiving crushed BIC/FTC/TAF, a film-coated FDC tablet, lacked PK measurements and described inconsistent virological outcomes.[57] Based on an adult bioequivalence study, crushed BIC/FTC/TAF may lead to suboptimal FTC and TAF exposures.[58] Thus, crushed BIC/FTC/TAF **is not recommended** (see the Bictegravir section for details).

For children who are unable to swallow a whole tablet, BIC/FTC/TAF may be split and each part taken separately, as long as all parts are swallowed within 10 minutes. Among 18 children aged ≥2 years and weighing 14 to <25 kg, 79% to 89% reported that BIC/FTC/TAF tablets were easy or super easy to swallow. Of six children under 6 years old who split the tablet in half on at least one occasion, three were swallowing the tablet whole at Week 48.[54] Among 24 children with HIV-1 aged ≥6 years to <12 years and weighing ≥25 kg to <40 kg swallowing FDC tablets of DRV/c/FTC/TAF or who split matching placebo tablets, 96% were able to swallow the whole or split tablet after one or two attempts, and >70% rated acceptability for long-term daily use as acceptable or good. Breaking the scored matching placebo was considered easy or OK by 79% of caregivers, although whole tablets were favored over split tablets among children.[59]

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF.[25-27,30-33,60,61] 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.[25] These differences were maintained until 96 weeks.[28] The clinical importance of these changes in BMD is unclear. Preliminary data from two open-label multicohort studies of 169 ART-naive or ART-experienced children and adolescents living with HIV aged ≥2 years and weighing ≥14 kg who received TAF/FTC-containing ART were reassuring with respect to longitudinal (up to 144 to 288 weeks) BMD measurements.[62] Dual-energy x-ray absorptiometry of the spine and total body less head (TBLH) BMD measurements increased from baseline over time, and height-adjusted z-scores also increased from baseline, except for a decrease in height-adjusted TBLH z-scores in the youngest and lightest

female group. One participant had a >4% decrease in spine BMD, but none had a >4% decrease in TBLH density. The increases in spine and TBLH BMD were consistent with those observed in children and adolescents without HIV.

Renal

Studies in adolescents aged 12 to 17 years[38] and adults[25-27,30,31,33] show that TAF is less frequently associated with glomerular and renal tubular damage than TDF.[63] 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.[25] These differences persisted until 96 weeks of follow-up.[28] Safety of EVG/c/FTC/TAF has been demonstrated in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.[64] Postmarketing cases of renal impairment—including acute renal failure, proximal renal tubulopathy, and Fanconi syndrome—have been reported with TAF-containing products.[2,3] 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-naive 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.[65] 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.[31] Monitoring serum lipids while the patient is taking TAF-containing FDC tablets is warranted, given these data (see Table 17b. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Dyslipidemia for details).

Weight Gain

Observational data are limited, and no randomized controlled trials have examined TAF-associated weight gain in children. In adults, greater weight gain has been reported with the use of TAF than with the use of TDF[66-73] (see Table 17h. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain for details). Although weight gain at ART initiation might represent a “return to health,”[63] patients initiating treatment with TAF had larger increases in weight than those initiating treatment with TDF[67,68]; increases in weight and body mass index (BMI) have been observed in ARV switch studies, as well.[69,72,74] In adults, the effect may be greatest in Black females,[68,72] especially if administered in combination with INSTIs.[68,70] A study in adult women showed increased BMI with the switch to either an INSTI or TAF, but these BMI increases were only seen in people with BMI <30 kg/m^2 at baseline.[66]

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