

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



Developed by the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

## How to Cite the Pediatric Antiretroviral Guidelines:

Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Department of Health and Human Services. Available at <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv>. Accessed (insert date) [include page numbers, table number, etc., if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (<https://clinicalinfo.hiv.gov/>).

# Appendix A: Pediatric Antiretroviral Drug Information

## Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC, Epivir)

Tenofovir Alafenamide (TAF, Vemlidy)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, Retrovir)

# Abacavir (ABC, Ziagen)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Pediatric Oral Solution:</b> 20 mg/mL</p> <p><b>Tablet:</b> 300 mg (scored)</p> <p><b>Generic Formulations</b></p> <ul style="list-style-type: none"> <li>• 300-mg tablet</li> <li>• 20-mg/mL pediatric oral solution</li> </ul> <p><b>Fixed-Dose Combination Tablets</b></p> <ul style="list-style-type: none"> <li>• [Epzicom and generic] Abacavir 600 mg/lamivudine 300 mg</li> <li>• [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg</li> <li>• [Triumeq PD] Abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg</li> </ul> <p>When using fixed-dose combination (FDC) tablets, refer to other sections of <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-Packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonate (Aged Birth Through &lt;1 Month) Dose</b></p> <p><i>Oral Solution</i></p> <ul style="list-style-type: none"> <li>• Abacavir (ABC) is not approved by the U.S. Food and Drug Administration (FDA) for use in infants aged &lt;3 months.</li> <li>• <b>However</b>, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends ABC 2 mg/kg twice daily for full-term infants from birth through &lt;1 month of age. This recommendation is based on data from pharmacokinetic (PK) modeling of neonatal ABC dosing to target adult plasma ABC exposures, and observational data supporting safety of ABC in neonates. The World Health Organization <a href="#">Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring</a> Annex 1: Dosages for ARV Drugs provides weight-band dosing recommendations for full-term neonates based on the same data. See the Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below.</li> </ul> <p><b>Infant (Aged ≥1 Month to &lt;3 Months) Dose</b></p> <p><i>Oral Solution</i></p>	<ul style="list-style-type: none"> <li>• Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough, shortness of breath).</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>• To predict the risk of HSRs, test patients for the HLA-B*5701 allele before starting therapy. Patients who test positive for the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.</li> <li>• Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires <b>immediate and permanent discontinuation of ABC. Do not rechallenge.</b></li> <li>• ABC <b>and coformulated tablets</b> can be given <b>with or</b> without food. The oral solution does not require refrigeration.</li> </ul>

- ABC is not approved by the FDA for use in infants aged <3 months.
- The Panel recommends ABC 4 mg/kg twice daily in full-term infants aged  $\geq 1$  month to <3 months. This recommendation is based on modeling data of the ABC 4 mg/kg twice-daily dose using PK simulation for full-term infants aged  $\geq 1$  month to <3 months. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 study and two observational cohorts provide reassuring data on the safety of ABC in infants with HIV aged <3 months. See the Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below.

### Infant and Child (Aged $\geq 3$ Months) Dose

#### Oral Solution

- ABC 8 mg/kg twice daily (maximum 300 mg per dose) or ABC 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. The ABC dose can be changed from twice daily to once daily with the liquid formulation to harmonize with other antiretroviral drugs administered once daily.

### Weight-Band Dosing of ABC Tablets for Children and Adolescents Weighing $\geq 14$ kg and <25 kg

Weight	Scored 300-mg ABC Tablet		
	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
$\geq 20$ kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)

### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose

- ABC 300 mg twice daily or ABC 600 mg once daily

#### [Epzicom] Abacavir/Lamivudine

#### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose

- One tablet once daily

#### [Triumeq PD] Abacavir/Dolutegravir (DTG)/Lamivudine (3TC)

#### Child Weighing $\geq 6$ kg to <25 kg and Aged $\geq 3$ Months

- Dispersible Triumeq PD tablets are FDA approved for children aged  $\geq 3$  months and weighing  $\geq 6$  to <25 kg. Triumeq PD is not recommended for children weighing  $\geq 25$  kg who are eligible for adult Triumeq dosing.

- For ABC/DTG/3TC dispersible tablets, fully disperse them in 20 mL of drinking water in the supplied cup and swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure that the child takes the full dose and that no medication remains in the dosing cup. ABC/DTG/3TC dispersible tablets should not be swallowed whole, chewed, cut, or crushed.
- Screen patients for hepatitis B virus (HBV) infection before using ABC FDC tablets that contain 3TC. Severe acute exacerbation of HBV infection can occur when 3TC is discontinued (see [Lamivudine](#)).

### Metabolism/Elimination

- ABC is systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.
- The majority of ABC is excreted as metabolites in urine.

### Abacavir Dosing in Patients with Hepatic Impairment

- ABC requires a dose adjustment in patients with mild hepatic insufficiency and is contraindicated with moderate or severe hepatic insufficiency.
- **Do not use** Epzicom, Triumeq PD, or Triumeq (or the generic equivalents of these FDC tablets) in patients with impaired hepatic function because the dose of ABC cannot be adjusted.

### Abacavir Dosing in Patients with Renal Impairment

- ABC does not require dose adjustment in patients with renal impairment.
- **Do not use** FDC tablets containing 3TC (Epzicom, Triumeq PD, Triumeq, or the generic equivalents of these FDC tablets) in patients with creatinine clearance (CrCl) <30 mL/min or patients on dialysis, because the doses of 3TC cannot be adjusted. Data from FDC DTG/3TC (Dovato) suggest that patients with a sustained CrCl of 30–49 mL/min may experience a higher 3TC exposure and should be monitored for hematologic toxicities and potential FDC discontinuation and subsequent adjustment of the treatment regimen. See package inserts for additional information.

- Administer the appropriate number of tablets once daily dispersed in 15-20 mL of water. See Special Instructions below. Triumeq PD tablets should not be swallowed whole, chewed, cut, or crushed.

**Weight-Band Dosing of Triumeq PD Tablets for Children Weighing  $\geq 6$  kg and  $< 25$  kg**

Weight	Recommended Daily Dose	Number of Triumeq PD Tablets
6 kg to $< 10$ kg <sup>a</sup>	ABC 180 mg DTG 15 mg 3TC 90 mg	3 <sup>a</sup>
10 kg to $< 14$ kg	ABC 240 mg DTG 20 mg 3TC 120 mg	4
14 kg to $< 20$ kg	ABC 300 mg DTG 25 mg 3TC 150 mg	5
20 kg to $< 25$ kg	ABC 360 mg DTG 30 mg 3TC 180 mg	6

<sup>a</sup>In infants weighing 6 to  $< 10$  kg dosing only requires 15 mL water.

- For use in children who are antiretroviral (ARV) naive or ARV experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) or cytochrome P450 (CYP) 3A inducers.

**[Triumeq] Abacavir/Dolutegravir/Lamivudine**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose*

- One tablet once daily
- This FDC tablet can be used in patients who are ARV-naive or ARV experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with other drugs that act as UGT1A1 or CYP3A inducers.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Abacavir (ABC) neither inhibits nor is metabolized by hepatic cytochrome P450 enzymes. Therefore, it does not cause significant changes in the clearance of agents, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), that are metabolized through these pathways.

- ABC plasma concentrations can decrease when ABC is used concurrently with the ritonavir-boosted PIs atazanavir/ritonavir, lopinavir/ritonavir (LPV/r), and darunavir/ritonavir.<sup>1-3</sup> The mechanism and the clinical significance of the drug interactions with these PIs are unknown. Currently, no recommendations exist for dose adjustments when ABC is coadministered with one of these boosted PIs.
- In the pooled analysis of 230 African children with HIV with a median age of 2.1 years (range 0.1–12.8) and a median weight of 9.8 kg (range 2.5–30.0), the population pharmacokinetics (PK) of ABC showed that children on boosted PI LPV/r or NNRTI efavirenz (EFV) had similar ABC exposures, while concomitant tuberculosis treatment and use of super-boosting with LPV significantly reduced ABC concentrations.<sup>4</sup>
- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) interferes with ABC metabolism; it affects the activity of alcohol dehydrogenase and glucuronyl transferase. This interference increased ABC area under the curve (AUC) plasma exposure by 41% in adult men with HIV who received ABC 600 mg daily.<sup>5</sup>
- ABC oral solution contains sorbitol, which decreased the exposure of lamivudine (3TC) oral solution in adults when the drugs were administered concurrently.<sup>6</sup> The clinical significance of this interaction is unknown.

## Major Toxicities

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, anorexia
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) have been observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving ABC. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of ABC. The risk of an ABC HSR is associated with the presence of the HLA-B\*5701 allele; the risk is greatly reduced by not using ABC in those who test positive for the HLA-B\*5701 allele. The HSR to ABC is a multiorgan clinical syndrome usually characterized by rash, or signs or symptoms in two or more of the following groups:
  - Fever
  - Constitutional symptoms, including malaise, fatigue, or achiness
  - Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhea, or abdominal pain
  - Respiratory signs and symptoms, including dyspnea, cough, or pharyngitis
  - Laboratory and radiologic abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis—including fatal cases—also have been reported. Pancreatitis with laboratory abnormalities can occur.

If an HSR is suspected, ABC **should be stopped immediately and not restarted because hypotension and death may occur upon rechallenge.**
- *Rare:* Increased levels of liver enzymes, elevated blood glucose levels, elevated triglycerides (see information on cardiovascular risk below). Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis—including fatal cases—have been reported.

- *Rare*: Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome.

## 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*

ABC is approved by the U.S. Food and Drug Administration (FDA) for use in children with HIV aged  $\geq 3$  months as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, provides dosing guidance for ABC as a component of the NRTI backbone for full-term neonates starting at birth and weighing  $\geq 2$  kg (see Annex 1: Dosages for ARV Drugs in the WHO [Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring](#)). The WHO guidance for ABC dosing in neonates increases the choices of antiretroviral (ARV) agents for the management of newborns in special situations where stock outs of nevirapine or zidovudine (ZDV) may affect the ability to effectively provide postnatal prophylaxis or treatment of neonatal HIV. The WHO recommendation of ABC dosing for infants starting at 1 month of age is based on the inclusion of ABC as a preferred NRTI component of the first- and second-line ARV regimens for children in the WHO [Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring](#). This recommendation also takes into account the availability of the President’s Emergency Plan for AIDS Relief (PEPFAR) tentatively approved pediatric generic ABC formulations—including coformulations that include 3TC—and the cost of ARV drugs in resource-limited settings.

### Efficacy

Both the once-daily and twice-daily doses of ABC have demonstrated durable antiviral efficacy in pediatric clinical trials that is comparable to the efficacy observed for other NRTIs in children.<sup>7-11</sup> In an observational study of nine cohorts from the International Epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration, 6- and 12-month viral suppression (<400 copies/mL) rates were evaluated among infants who initiated ART at age <3 months, and were compared with infants aged <28 and  $\geq 28$  days and weighing <3 and  $\geq 3$  kg at the time of ART initiation. Viral suppression at 12 months did not differ by age or weight at the time of ART initiation and it was slightly lower in infants on ABC (174/329 [53%]) versus in those on ZDV (77/138 [56%]) (adjusted odds ratio 1.8; 95% confidence interval (CI) 1.0–3.2).<sup>12</sup>

## Pharmacokinetics

### *Pharmacokinetics in Neonates and Infants*

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 trial reported PK data in 25 infants aged <3 months with HIV who were initiated on a median ABC dose of 10 mg/kg (range, 6–13 mg/kg) twice daily in combination with 3TC and LPV/r after 1 month of

life. Median age was 6 weeks (range, 1.5–11 weeks); median weight was 2,250 g (range 1,360–3,320 g); median gestational age was 36 weeks (range, 27–39 weeks). Sparse and pre-dose PK ABC samples were repeatedly obtained throughout 24 weeks of study follow-up. ABC plasma exposures were high compared to the published data in infants aged >3 months and decreased rapidly between 2 and 8 months of age as the infants matured and ABC clearance increased.<sup>13</sup> In the Tygerberg cohort study from South Africa, 10 healthy term neonates at the median postnatal age of 10 days (range 6–15) who were administered a single ABC dose of 8 mg/kg before 15 days of life had substantially higher exposures than in infants and children and no reported adverse events.<sup>14</sup> Higher ABC exposures in neonates than in infants and children are likely due to slower drug clearance through immature enzyme pathways.

PK modeling of ABC starting at birth has been conducted using pooled data from 308 ABC concentration measurements obtained from three studies administering ABC liquid to 45 young infants (including 21 full-term neonates <15 days of age with intensive PK).<sup>14</sup> Two of these studies, the Pediatric AIDS Clinical Trials Group (PACTG) 321 study and the Tygerberg cohort, performed intensive PK sampling in full-term neonates receiving ABC for HIV prophylaxis. The third study, IMPAACT P1106, described above, performed sparse PK sampling on full-term and low birth weight (LBW; <2,500 g) infants with HIV. LBW infants were older at the first PK assessment, with a median postnatal age of 73 days (range 41–190) and weight of 3.8 kg (range 2.4–5.8). ABC PK parameters in neonates were estimated using PK simulations to achieve plasma ABC exposures (area under the curve from time zero to 12 hours after drug administration; AUC<sub>0–12</sub>) within the expected adult range (3.2–25.2 mcg•hr/mL). The PK model predicted a slow ABC clearance of 2.51 mL/min per kg at birth, which doubled by 4 weeks of age. Simulations predicted that an ABC dose of 2 mg/kg twice daily in full-term neonates from birth to <4 weeks and an ABC dose of 4 mg/kg twice daily in infants aged 4 to 12 weeks would achieve target AUC<sub>0–12</sub>; however, data in LBW infants are lacking.<sup>14</sup> Based on these data, the weight-band dosing of ABC for neonates has been developed for neonates from birth to age <1 month and is included in the WHO [Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring](#).<sup>15</sup> This weight-band dosing for neonates approximates the ABC dosing per kg based on the postnatal age (see [Table 1](#) below).



**Table 1. Simplified Weight-Band Dosing for Full-Term Neonates from Birth to <1 Month of Age (WHO [Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring Annex 1: Table A1.4](#))**

Birth to <1 Month of Age		
Weight	Volume of ABC Oral Solution 20 mg/mL Twice Daily <sup>a,b</sup>	ABC Dose in mg Twice Daily (ranges mg/kg, from lowest to highest weight within the weight band) <sup>a,b</sup>
2 kg to <3 kg	0.4 mL	8 mg (4.0–2.8 mg/kg)
3 kg to <4 kg	0.5 mL	10 mg (3.3–2.6 mg/kg)
4 kg to <5 kg	0.6 mL	12 mg (3.0–2.4 mg/kg)

<sup>a</sup> Simplified weight-band dosing exceeds recommended mg/kg ABC dosing in neonates and infants.

<sup>b</sup> Neonatal ABC dose is based on birth weight and does not require weight-based adjustment during the first month of life.

Key: ABC = abacavir

For infants aged  $\geq 1$  month with weight 3 to <6 kg, the WHO [Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring](#) currently recommend a twice-daily dose of 3 mL (60 mg) of ABC 20 mg/mL solution (range 10–20 mg/kg/dose). The weight-band dosing for neonates and infants within the WHO HIV guidelines is higher than the modeled weight-based dosing for practical considerations in resource-limited settings. As new generic pediatric formulations of ABC become available in resource-limited settings, there is potential for the revision of the WHO guidelines for weight-band dosing of ABC for young infants.

Based on the PK modeling from three infant studies<sup>14</sup> and the neonatal and infant safety data from the IMPAACT 1106 study and two observational cohort studies (see Safety in Neonates and Infants below), the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends an ABC dose of 2 mg/kg twice daily for neonates from birth to <1 month of age and an ABC dose of 4 mg/kg twice daily for full-term infants aged  $\geq 1$  month and <3 months.

## Pharmacokinetics in Children

PK studies of ABC in children aged <12 years have demonstrated that metabolic clearance of ABC in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.<sup>16</sup>

The PKs of ABC administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover open-label PK trials of twice-daily versus once-daily dosing of ABC and 3TC (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).<sup>5,17-20</sup> The data from these three pediatric trials were used to develop a model for ABC PKs; this model predicted that systemic plasma ABC exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged  $\leq 12$  years.<sup>17-21</sup> Both the trials and PK modeling have demonstrated that once-daily dosing with either the tablet or the liquid formulation of ABC produces plasma exposures comparable to those seen with a twice-daily dosing schedule that uses the same total daily dose of ABC.<sup>5</sup>

## Dosing

### *Dosing and Formulations*

A total daily dose of ABC 600 mg can be used safely in a person weighing 25 kg.<sup>5</sup> Doses of the liquid ABC formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use in younger children who are unable to swallow a pill.<sup>22</sup>

In the three ABC dosing pediatric trials described above,<sup>17-20</sup> only children who had low viral loads and who were clinically stable on the twice-daily dose of ABC were eligible to change to once-daily ABC dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily ABC (n = 336) versus twice-daily ABC (n = 333) in tablet form combined with a once-daily or twice-daily 3TC-based ARV regimen.<sup>11</sup> To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of the ABC liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of ABC at a dose of 16 mg/kg (with a maximum dose of ABC 600 mg) is recommended. However, twice-daily dosing is recommended for infants and young children who initiate therapy with the liquid formulation of ABC. Switching to once-daily dosing with the liquid formulation could be considered when harmonizing with other antiretroviral drugs administered once daily, such as 3TC and dolutegravir (DTG).

Recent data from the IMPAACT 2019 clinical trial of dispersible and immediate-release ABC/DTG/3TC tablets in children with HIV has validated the FDA-approved dosing in infants and children weighing 10 to <25 kg and established newly proposed dosing of this fixed-dose combination (FDC) (3 tablets once daily of ABC 60 mg, DTG 5 mg, and 3TC 30 mg dispersed in 15–20 mL of water) in infants aged ≥3 months weighing 6 to <10 kg. (Food and Drug Administration 2023) ABC/DTG/3TC dispersible FDC dosing was developed based on PK and safety data in each weight band at the originally selected dosing, which aligned with WHO weight band dosing for the individual ARV agents. Follow-up through 24 weeks confirmed the safety, tolerability, and virological efficacy of both formulations.<sup>23</sup>

## Toxicity

### *Safety in Neonates and Infants*

Data from the PACTG 321, the IMPAACT P1106 trial, and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including infants with weight <3 kg.<sup>12,13,24</sup> The IMPAACT P1106 trial reported 24 weeks of safety data in 27 infants in whom repeated dosing of ABC was initiated at the median age of 60 days. Fifteen infants (55.6%; 90% CI, 38.3–72.0) met the safety endpoint of death or a Grade 3 or higher adverse event (AE). None of the AEs were related to ABC, and none led to interruptions or adjustments of ABC dosing. No hypersensitivity reactions were reported with the multi-dose treatment.<sup>13</sup> In two cohorts of neonates (<1 month of age) who received a single ABC dose, ABC was well tolerated; all reported AEs in the PACTG 321 study were unrelated to ABC, and no AEs were reported in the Tygerberg cohort.<sup>14,25</sup> The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) reported safety outcomes among 139 children from 13 cohorts in 11 countries in Europe who initiated ABC at age <3 months. By 12 months on ABC, 3.6% (n = 4) had discontinued ABC because of an ART safety concern and 11.8% (n = 15) discontinued ABC for any reason.<sup>24</sup> Another observational study of nine cohorts from the IeDEA Southern Africa

collaboration compared safety outcomes (measured as ABC discontinuations and their reasons) between infants who started ABC aged <28 days (n = 232) and those aged ≥28 days (n = 605), and between infants who started ABC with weight <3 kg (n = 53) and those with weight ≥3 kg (n = 784) at the time of ABC initiation.<sup>12</sup> ABC discontinuations at 6 and 12 months were not significantly different in infants who started ART aged <28 days versus ≥28 days or in infants who weighed <3 kg versus ≥3 kg. ABC discontinuations were less frequent than ZDV discontinuations (adjusted hazard ratio 0.14, 95% CI 0.10–0.20).<sup>12</sup>

### ***Safety in Children and Adolescents***

ABC has less of an effect on mitochondrial function than the NRTI ZDV<sup>7,8</sup> and less bone and renal toxicity than tenofovir disoproxil fumarate.<sup>26,27</sup>

Systematic review and meta-analysis of the 54 full-text articles on the observational and experimental studies conducted in infants, children, and adolescents with HIV who are aged 10 to 19 years and that included data on safety, efficacy, or both, and were published in English or French between 2009 and 2022 reported that toxic effects due to ABC use in infants, children, and adolescents remain rare and manageable.<sup>28</sup>

Several observational cohort studies, including contemporary cohort analyses, suggest that an increased risk of cardiovascular disease (CVD) events—such as myocardial infarction, stroke, and invasive cardiovascular procedure—exists in adults who are currently using ABC or who have recently used ABC (see [Cardiovascular Risk in Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy in the Adult and Adolescent Guidelines](#)); however, other studies have not substantiated this finding. Limited data are available on the CVD risks associated with ABC use in children. One cohort study of South African adolescents (385 participants with HIV and 63 participants as HIV-negative controls) with a median age of 12 years reported an association between ABC exposure and insulin resistance, which was evaluated using homeostatic model assessment. These findings suggested that the use of ABC may be a CVD risk factor for young people with perinatally acquired HIV.<sup>29</sup> In a recent prospective study of 101 virally suppressed (≤400 copies/mL) youth aged 10 to 18 years with HIV and 97 uninfected controls from Uganda, the baseline common carotid artery intima-media thickness (IMT) was slightly higher in participants with HIV than in controls ( $P < 0.01$ ), and pulse wave velocity (PWV) did not differ between groups. In longitudinal analyses, the longer ART duration was associated with lower PWV in youth with HIV ( $\beta = .008$  [95% CI, -.008 to .003]), while ABC use was associated with greater IMT in youth with HIV ( $\beta = .043$  [95% CI, .012–.074]). These findings suggest that in adolescents with HIV, early prolonged ART may prevent progression of subclinical vascular disease, while prolonged ABC use may increase it.<sup>30</sup>

## Emtricitabine (FTC, Emtriva)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Pediatric Oral Solution:</b> 10 mg/mL</p> <p><b>Capsule:</b> 200 mg</p> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>• [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Biktarvy] <ul style="list-style-type: none"> <li>○ Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg</li> <li>○ Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg</li> </ul> </li> <li>• [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Descovy] <ul style="list-style-type: none"> <li>○ Emtricitabine 200 mg/tenofovir alafenamide 25 mg</li> <li>○ Emtricitabine 120 mg/tenofovir alafenamide 15 mg</li> </ul> </li> <li>• [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> <li>• [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg</li> <li>• [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> <li>• [Truvada] <ul style="list-style-type: none"> <li>○ Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>○ Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg</li> <li>○ Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg</li> <li>○ Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg</li> </ul> </li> </ul> <p>When using FDC tablets, refer to other sections of the <a href="#">Drug Appendix</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonatal and Infant (Aged 0 to &lt;3 Months) Dose</b></p> <p><i>Oral Solution</i></p> <ul style="list-style-type: none"> <li>• Emtricitabine (FTC) 3 mg/kg once daily</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperpigmentation/skin discoloration on palms and/or soles</li> </ul>

<p><b>Child (Aged ≥3 Months) and Adolescent Dose</b></p> <p><i>Oral Solution</i></p> <ul style="list-style-type: none"> <li>• FTC 6 mg/kg once daily (maximum 240 mg per dose). The maximum dose of oral solution is higher than the capsule dose because a pediatric pharmacokinetic analysis reported that the plasma exposure for FTC was 20% lower in patients who received the oral solution than in patients who received the capsule formulation.</li> </ul> <p><i>Capsules (for Patients Weighing &gt;33 kg)</i></p> <ul style="list-style-type: none"> <li>• FTC 200 mg once daily</li> </ul> <p><b>Adult Dose</b></p> <p><i>Oral Solution for Patients Who Are Unable to Swallow Capsules</i></p> <ul style="list-style-type: none"> <li>• FTC 240 mg (24 mL) once daily</li> </ul> <p><i>Capsules</i></p> <ul style="list-style-type: none"> <li>• FTC 200 mg once daily</li> </ul> <p><b>[Atripla and Generic] Efavirenz/FTC/Tenofovir Disoproxil Fumarate (TDF)</b></p> <p><i>Child and Adolescent (Weighing ≥40 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily</li> <li>• Take on an empty stomach.</li> </ul> <p><b>[Biktarvy] Bictegravir/FTC/Tenofovir Alafenamide (TAF)</b></p> <p><i>Neonate or Child (Aged &lt;2 Years and Weighing &lt;14 kg) Dose</i></p> <ul style="list-style-type: none"> <li>• No data are available on the appropriate dose of Biktarvy in children aged &lt;2 years and weighing &lt;14 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.</li> </ul> <p><i>Child, Adolescent, and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily, with or without food.</li> </ul> <table border="1" data-bbox="203 1423 852 1644"> <thead> <tr> <th>Body Weight</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>≥14 kg to &lt;25 kg</td> <td>Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg</td> </tr> <tr> <td>≥25 kg</td> <td>Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg</td> </tr> </tbody> </table>	Body Weight	Dose	≥14 kg to <25 kg	Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg	≥25 kg	Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg	<table border="1"> <tr> <th data-bbox="868 182 1421 268">Special Instructions</th> </tr> <tr> <td data-bbox="868 268 1421 724"> <ul style="list-style-type: none"> <li>• Although FTC can be administered without regard to food, some FDC tablet formulations that contain FTC have food requirements.</li> <li>• FTC oral solution can be kept at room temperature, up to 77°F (25°C), if used within 3 months; refrigerate oral solution for long-term storage.</li> <li>• Screen patients for hepatitis B virus (HBV) infection before using FTC or FDC tablets that contain FTC. Severe acute exacerbation of HBV infection can occur when FTC is discontinued; therefore, hepatic function and hepatitis B viral load should be monitored for several months after patients with HBV infection stop taking FTC.</li> </ul> </td> </tr> <tr> <th data-bbox="868 724 1421 798">Metabolism/Elimination</th> </tr> <tr> <td data-bbox="868 798 1421 955"> <ul style="list-style-type: none"> <li>• No CYP interactions</li> <li>• Eighty-six percent of FTC is excreted in urine. FTC may compete with other compounds that undergo renal elimination.</li> </ul> </td> </tr> <tr> <th data-bbox="868 955 1421 1018">FTC Dosing in Patients with Hepatic Impairment</th> </tr> <tr> <td data-bbox="868 1018 1421 1375"> <ul style="list-style-type: none"> <li>• Atripla should be used with caution in patients with hepatic impairment.</li> <li>• Biktarvy, Genvoya, Stribild, and Symtuza are not recommended for use in patients with severe hepatic impairment.</li> <li>• Complera, Descovy, and Odefsey do not require dose adjustment in mild or moderate hepatic impairment but should not be used in patients with severe hepatic impairment because they have not been studied in this group.</li> </ul> </td> </tr> <tr> <th data-bbox="868 1375 1421 1438">FTC Dosing in Patients with Renal Impairment</th> </tr> <tr> <td data-bbox="868 1438 1421 1789"> <ul style="list-style-type: none"> <li>• Decrease the dose of FTC in patients with impaired renal function. 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- The U.S. Food and Drug Administration approved Biktarvy for use only in antiretroviral therapy (ART)–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 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 and who have virus containing the M184V mutation.
- See the [Bictegravir](#) section for additional information.

**[Complera] FTC/Rilpivirine (RPV)/TDF**

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

- One tablet once daily in ART-naïve patients who have baseline plasma HIV RNA ≤100,000 copies/mL. This dose of Complera also can be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA <50 copies/mL) with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.
- Administer with a meal of at least 500 calories.

**[Descovy] FTC/TAF**

*Child and Adolescent and Adult Dose*

Body Weight	Dose
≥14 kg to <25 kg	FTC 120 mg/TAF 15 mg, 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 (CYP) 3A inhibitor (e.g., ritonavir [RTV] or 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.

- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- TAF-containing formulations are not recommended for use in patients with estimated CrCl <30 mL/min.

**[Genvoya] Elvitegravir/Cobicistat (COBI)/FTC/TAF**

*Child and Adolescent (Weighing  $\geq 25$  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/RPV/TAF**

*Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose*

- One tablet once daily in ART-naive patients with HIV RNA  $\leq 100,000$  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) with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

**[Stribild] Elvitegravir/COBI/FTC/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg with a Sexual Maturity Rating of 4 or 5) and Adult Dose*

- One tablet once daily with food in ART-naive patients. This dose of Stribild also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

**[Symtuza] Darunavir (DRV)/COBI/FTC/TAF**

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose*

- One tablet once daily with food in ART-naive patients or in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) with no known mutations associated with resistance to DRV or tenofovir.

**[Truvada] FTC/TDF**

**Truvada Dosing Table**

*Child, Adolescent, and Adult Dose*

Body Weight	FTC/TDF Tablet Once Daily
17 kg to $< 22$ kg	One FTC 100-mg/TDF 150-mg tablet
22 kg to $< 28$ kg	One FTC 133-mg/TDF 200-mg tablet
28 kg to $< 35$ kg	One FTC 167-mg/TDF 250-mg tablet
$\geq 35$ kg and adults	One FTC 200-mg/TDF 300-mg tablet



## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* **Do not use** emtricitabine (FTC) in combination with lamivudine (3TC), because these agents share similar resistance profiles and lack additive benefit. **Do not use FTC** with fixed-dose combination (FDC) medications that contain 3TC or FTC. See [Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class](#), and refer to other sections of the [Drug Appendix](#) for drug interaction information for each individual component of an FDC tablet.
- *Renal elimination:* FTC may compete with other compounds that undergo renal tubular secretion. Drugs that decrease renal function could decrease clearance of FTC.

## Major Toxicities

- *More common:* Headache, insomnia, diarrhea, nausea, rash. Hyperpigmentation/skin discoloration, which may be more common in children than in adults.
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in patients with hepatitis B virus (HBV)/HIV coinfection who switched from regimens that included FTC to regimens that did not include FTC.

## Resistance

The International Antiviral Society–USA maintains a list of [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

FTC is approved by the U.S. Food and Drug Administration for once-daily administration in children, starting at birth. FTC often is used as part of a dual-NRTI backbone in antiretroviral (ARV) regimens for children and adolescents because of its once-daily dosing, minimal toxicity, and favorable pediatric pharmacokinetic (PK) data.

## Efficacy and Pharmacokinetics

### *Comparative Clinical Trials*

Studies that assess the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned with the dynamic components of the regimen—such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide, or abacavir—than the more static components, such as FTC or 3TC. FTC and 3TC have been considered interchangeable, but data to support this conclusion are lacking. Investigators studying the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort



compared the efficacy of TDF plus FTC with TDF plus 3TC when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in antiretroviral therapy (ART)-naïve patients.<sup>1</sup> The adjusted hazard ratio for the virologic failure of 3TC-containing regimens compared with FTC-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). No difference between these regimens was observed in the time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. A Swiss cohort study found a potential difference in efficacy between FTC and 3TC; however, the difference disappeared after adjusting for pill burden.<sup>2</sup> Current evidence suggests that FTC and 3TC have equivalent efficacy and toxicity in ARV-naïve patients.

## ***Efficacy***

Following a dose-finding study (described in the Pharmacokinetics: Liquid Versus Capsule section below),<sup>3</sup> a once-daily dose of FTC 6 mg/kg administered in combination with other ARV drugs was studied in 116 patients aged 3 months to 16 years.<sup>4</sup> The study used a maximum dose of 240 mg of the FTC liquid formulation. PK results showed that the plasma exposures seen in these children and adolescents were similar to those seen in adults who received FTC 200 mg once daily. Follow-up data extending to Week 96 indicated that 89% of ART-naïve children and 76% of ARV-experienced children maintained plasma HIV RNA <400 copies/mL (75% of ARV-naïve children and 67% of ARV-experienced children had HIV RNA <50 copies/mL). Minimal toxicity was observed during this trial. Pediatric AIDS Clinical Trials Group (PACTG) P1021<sup>5</sup> evaluated the use of FTC 6 mg/kg (with a maximum dose of FTC 200 mg per day of the liquid formulation) as part of a three-drug regimen dosed once daily to ARV-naïve children aged 3 months to 21 years. In this trial, 85% of children achieved HIV RNA <400 copies/mL, and 72% of children maintained virologic suppression (HIV RNA <50 copies/mL) through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm<sup>3</sup> at Week 96.

## ***Pharmacokinetics: Liquid Versus Capsule***

A single-dose PK study of the FTC oral solution and FTC capsules enrolled 25 children with HIV aged 2 years to 17 years.<sup>3</sup> FTC was found to be well absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7–11.6 hours). Plasma concentrations in children who received the once-daily dose of FTC 6 mg/kg were approximately equivalent to those seen in adults who received the standard dose of FTC 200 mg. However, plasma concentrations of FTC after administration of the capsule formulation were approximately 20% higher than those observed after administration of the oral solution in this small cohort of children.

## ***Pharmacokinetics in Infants***

A study in South Africa evaluated the PK of FTC in 20 infants aged <3 months with perinatal HIV exposure. The participants received a dose of FTC 3 mg/kg once daily for two 4-day courses, separated by an interval of  $\geq 2$  weeks.<sup>6</sup> FTC exposure (area under the curve [AUC]) in neonates receiving FTC 3 mg/kg once daily was within the range of exposures seen in pediatric patients aged >3 months who received the recommended dose of FTC 6 mg/kg once daily and adults who received the recommended dose of FTC 200 mg once daily. During the first 3 months of life, FTC AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (n = 6) who received a single dose of FTC 3 mg/kg and whose mothers received a single dose of FTC 600 mg during delivery, the FTC AUC exceeded the AUC seen in adults and older children. However, FTC had a half-life of 9.2 hours in these neonates, which is

similar to that observed in adults and older children.<sup>7</sup> Extensive safety data are lacking for this age range.

### ***Considerations for Use***

The FTC oral solution has an advantage over the liquid formulation of 3TC because it can be given once daily at ARV initiation, whereas the liquid formulation of 3TC needs to be given twice daily at ARV initiation. When pill formulations of 3TC or FTC are used, they can be administered once daily.

Both FTC and 3TC have antiviral activity and efficacy against HBV. For a comprehensive review of this topic, see the [Hepatitis B Virus](#) section in the [Pediatric Opportunistic Infection Guidelines](#).

## Lamivudine (3TC, Epivir)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations
<b>Pediatric Oral Solution</b> <ul style="list-style-type: none"><li>• [Epivir] 10 mg/mL</li><li>• [Epivir HBV]<sup>a</sup> 5 mg/mL</li></ul>
<b>Tablets</b> <ul style="list-style-type: none"><li>• [Epivir] 150 mg (scored) and 300 mg</li><li>• [Epivir HBV]<sup>a</sup> 100 mg</li></ul>
<b>Generic Formulations</b> <ul style="list-style-type: none"><li>• 100-mg, 150-mg, and 300-mg tablets</li></ul>
<b>Fixed-Dose Combination (FDC) Tablets</b> <ul style="list-style-type: none"><li>• [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li><li>• [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg</li><li>• [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li><li>• [Dovato] Dolutegravir 50 mg/lamivudine 300 mg</li><li>• [Epzicom] Abacavir 600 mg/lamivudine 300 mg</li><li>• [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li><li>• [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li><li>• [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li><li>• [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg</li><li>• [Triumeq PD] Abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg</li><li>• [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg</li></ul>
<p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p>
<p>For additional information, see <a href="mailto:Drugs@FDA">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>

Dosing Recommendations	Selected Adverse Events												
<p><b>Note:</b> See <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection</a> and <a href="#">Table 13: Antiretroviral Dosing Recommendations for Newborns</a> for information about using lamivudine (3TC) to prevent perinatal HIV transmission.</p> <p><b>Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to &lt;4 Weeks) Dose</b></p> <p><i>Oral Solution</i></p> <ul style="list-style-type: none"> <li>• 3TC 2 mg/kg twice daily</li> </ul> <p><b>Infant and Child Dose</b></p> <ul style="list-style-type: none"> <li>• Once-daily dosing of the 3TC oral solution is <b>not recommended</b> when initiating 3TC oral solution in infants and young children. Patients can be transitioned to once-daily treatment with the oral solution when they have been stable on twice-daily treatment for 36 weeks and are aged ≥3 years. Please see the note below and refer to the text for more detail.</li> </ul> <p><i>Aged ≥4 Weeks to &lt;3 Months</i></p> <ul style="list-style-type: none"> <li>• 3TC 4 mg/kg twice daily of the oral solution</li> </ul> <p><i>Aged ≥3 Months to &lt;3 Years</i></p> <ul style="list-style-type: none"> <li>• 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)</li> </ul> <p><i>Aged ≥3 Years</i></p> <ul style="list-style-type: none"> <li>• 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose); <i>or</i></li> <li>• 3TC 10 mg/kg once daily of the oral solution (maximum 300 mg per dose)</li> </ul> <p><b>Weight-Band Dosing for the 10-mg/mL 3TC Oral Solution in Children Weighing ≥3 kg</b></p> <table border="1" data-bbox="203 1386 893 1654"> <thead> <tr> <th>Weight</th> <th>Twice-Daily Dose, AM</th> <th>Twice-Daily Dose, PM</th> </tr> </thead> <tbody> <tr> <td>3 kg to &lt;6 kg</td> <td>3 mL</td> <td>3 mL</td> </tr> <tr> <td>6 kg to &lt;10 kg</td> <td>4 mL</td> <td>4 mL</td> </tr> <tr> <td>10 kg to &lt;14 kg</td> <td>6 mL</td> <td>6 mL</td> </tr> </tbody> </table> <p><i>Weighing ≥14 kg and Able to Swallow Tablets</i></p> <ul style="list-style-type: none"> <li>• Weight-band dosing (see table below; dose is approximately 3TC 5 mg/kg per day twice daily or 3TC 10 mg/kg once daily)</li> <li>• The scored tablet is the preferred formulation for pediatric patients weighing ≥14 kg who can swallow a tablet.</li> </ul>	Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM	3 kg to <6 kg	3 mL	3 mL	6 kg to <10 kg	4 mL	4 mL	10 kg to <14 kg	6 mL	6 mL	<ul style="list-style-type: none"> <li>• Headache</li> </ul> <p style="text-align: center;"><b>Special Instructions</b></p> <ul style="list-style-type: none"> <li>• 3TC and coformulated tablets can be given with and without food.</li> <li>• Store 3TC oral solution at room temperature.</li> <li>• For abacavir (ABC)/dolutegravir (DTG)/3TC dispersible tablets, fully disperse them in 20 mL of drinking water in the supplied cup and swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure that the child takes the full dose and no medication remains in the dosing cup. ABC/DTG/3TC dispersible tablets should not be swallowed whole, chewed, cut, or crushed.</li> <li>• Screen patients for hepatitis B virus (HBV) infection before using 3TC or FDC tablets that contain 3TC. Severe acute exacerbations of HBV can occur after discontinuation of 3TC. Hepatic function and HBV viral load should be monitored for several months after patients with HBV infection stop taking 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.</li> <li>• For any FDC tablet containing ABC, test patients for the HLA-B*5701 allele before starting therapy to predict the risk of hypersensitivity reactions. Patients who test positive for the HLA-B*5701 allele should not be given an ABC-containing FDC. Patients with no prior HLA-B*5701 testing who are tolerating an ABC-containing regimen do not need to be tested. See <a href="#">Abacavir</a>.</li> </ul>
Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM											
3 kg to <6 kg	3 mL	3 mL											
6 kg to <10 kg	4 mL	4 mL											
10 kg to <14 kg	6 mL	6 mL											
	<p style="text-align: center;"><b>Metabolism/Elimination</b></p> <p><b>3TC Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>• No change in 3TC dosing is required for patients with hepatic impairment.</li> <li>• FDC tablets containing ABC or ZDV should not be used in patients who have impaired hepatic function.</li> </ul>												

**Weight-Band Dosing for the Scored, 150-mg 3TC Tablet in Children Weighing  $\geq 14$  kg**

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (75 mg)	½ tablet (75 mg)	1 tablet (150 mg)
$\geq 20$ kg to <25 kg	½ tablet (75 mg)	1 tablet (150 mg)	1½ tablets (225 mg)
$\geq 25$ kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets (300 mg)

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching from twice-daily dosing to once-daily dosing of 3TC (using the oral solution or tablets) in children aged  $\geq 3$  years who have been clinically stable for 36 weeks with undetectable viral loads and stable CD4 T lymphocyte cell counts. Clinicians should choose a once-daily regimen using the once-daily dose of 3TC indicated above (approximately 3TC 10 mg/kg, with a maximum of 3TC 300 mg once daily).

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose*

- 3TC 150 mg twice daily; or
- 3TC 300 mg once daily

**[Cimduo] 3TC/Tenofovir Disoproxil Fumarate (TDF)**

*Child and Adolescent (Weighing  $> 35$  kg) and Adult Dose*

- One tablet once daily

**[Combivir and Generic] 3TC/Zidovudine (ZDV)**

*Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose*

- One tablet twice daily

**[Delstrigo] Doravirine/3TC/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose*

- One tablet once daily in antiretroviral (ARV)-naive patients and ARV-experienced 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 Delstrigo

**[Dovato] DTG/3TC**

*Adult Dose*

- One tablet once daily with or without food as a complete ARV regimen in antiretroviral therapy (ART)-naive adults with no known mutations associated with resistance to the individual components of Dovato

- Symfi and Symfi Lo should be used with caution in patients with hepatic impairment; Symfi and Symfi Lo are not recommended for use in moderate or severe hepatic impairment.
- Delstrigo and Dovato do not require dose adjustment in mild or moderate hepatic impairment but have not been studied in patients and so are not recommended with severe hepatic impairment.

**3TC Dosing in Patients with Renal Impairment**

- Dose adjustment of 3TC is required for patients with renal insufficiency.
- Do not use FDC tablets containing 3TC in patients with creatinine clearance  $< 30$  mL/min or patients on dialysis, because the doses of 3TC cannot be adjusted. Data from the FDC DTG/3TC (Dovato) suggest that patients with a sustained creatinine clearance 30–49 mL/min may experience a higher 3TC exposure and should be monitored for hematologic toxicities and potential FDC discontinuation and subsequent adjustment of the treatment regimen. See package inserts for additional information.

- Dovato is not approved by the U.S. Food and Drug Administration (FDA) or recommended by the Panel for use in children or adolescents as a complete ARV regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug.

**[Epzicom] ABC/3TC**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose*

- One tablet once daily

**[Symfi] Efavirenz (EFV) 600 mg/3TC/TDF**

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose*

- One tablet once daily on an empty stomach

**[Symfi Lo] EFV 400 mg/3TC/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose*

- One tablet once daily on an empty stomach
- Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh  $\geq 40$  kg. The use of therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh  $\geq 40$  kg (see the [Efavirenz](#) section for more information).

**[Temixys] 3TC/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose*

- One tablet once daily

**[Triumeq PD] ABC/DTG/3TC**

*Child Weighing  $\geq 10$  kg to  $< 25$  kg*

- Dispersible Triumeq PD tablets are FDA approved for children weighing  $\geq 10$  to  $< 25$  kg. Triumeq PD is not recommended for children weighing  $\geq 25$  kg who are eligible for adult Triumeq dosing.
- Administer the appropriate number of tablets for a child's weight once daily, dispersed in 20 mL of water. See Special Instructions. Triumeq PD tablets should not be swallowed whole, chewed, cut, or crushed.

**Weight-Band Dosing of Triumeq PD Tablets for Children Weighing  $\geq 6$  kg**

Weight	Recommended Daily Dose	Number of Triumeq PD Tablets
6 kg to $< 10$ kg*	ABC 180 mg DTG 15 mg 3TC 90 mg	3

<b>10 kg to &lt;14 kg</b>	ABC 240 mg DTG 20 mg 3TC 120 mg	4
<b>14 kg to &lt;20 kg</b>	ABC 300 mg DTG 25 mg 3TC 150 mg	5
<b>20 kg to &lt;25 kg</b>	ABC 360 mg DTG 30 mg 3TC 180 mg	6
<b>≥25 kg</b>	Use Triumeq (see below)	

\* Investigational dose (see above).

- For use in children who are ARV-naive or ARV-experienced (but integrase strand transfer inhibitor [INSTI]-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) or cytochrome P450 (CYP) 3A inducers

**[Triumeq] ABC/DTG/3TC**  
*Child and Adolescent (Weighing ≥25 kg) and Adult Dose*

- One tablet once daily
- This FDC tablet can be used in patients who are ART-naive or ART-experienced (but INSTI-naive) and who are not being treated with UGT1A1 or CYP3A inducers.

**[Trizivir and Generic] ABC/3TC/ZDV**  
*Child and Adolescent (Weighing ≥30 kg) and Adult Dose*

- One tablet twice daily

<sup>a</sup> Eпивir HBV oral solution and tablets contain a lower amount of 3TC than Eпивir oral solution and tablets. The amount of 3TC in the Eпивir HBV solution and tablet was based on dosing for treatment of HBV infection in people without HIV coinfection. Patients with HIV who are taking Eпивir HBV as part of their ARV regimen should receive the appropriate amount of oral solution or the appropriate number of tablets to achieve the higher doses of 3TC that are used to treat HIV.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Drugs that decrease renal function could decrease clearance of lamivudine (3TC).
- Do not use** 3TC in combination with emtricitabine (FTC), because these drugs have similar resistance profiles and using them together offers no additional benefit.<sup>1</sup> **Do not use** 3TC with fixed-dose combination (FDC) medications that contain 3TC or FTC. Please see [Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class](#) and refer to other sections of the [Drug Appendix](#) for drug interaction information about each individual component of FDC tablets.

## Major Toxicities

- More common:* Headache, nausea

- *Less common (more severe)*: Peripheral neuropathy, lipodystrophy/lipoatrophy
- *Rare*: Increased levels of liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

## Resistance

The International Antiviral Society–USA maintains a list of [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

Although 3TC is approved by the U.S. Food and Drug Administration (FDA) for the treatment of children aged  $\geq 3$  months, both the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) and the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission recommend the use of 3TC from birth.

### *Considerations for Use*

The efficacy and toxicity of 3TC are equivalent to the efficacy and toxicity of FTC. The oral formulation of FTC has an advantage over the liquid formulation of 3TC because it can be given once daily at antiretroviral (ARV) initiation, whereas the liquid formulation of 3TC needs to be given twice daily at ARV initiation. When pill formulations of 3TC or FTC are used, they can be administered once daily.

### *Comparative Clinical Trials*

Investigators studying the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort compared the efficacy of tenofovir disoproxil fumarate (TDF) plus FTC to TDF plus 3TC when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ART-naïve patients.<sup>2</sup> The adjusted hazard ratio for the virologic failure of 3TC-containing regimens compared to FTC-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). These regimens had no difference in time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. In a Swiss cohort, Yang et al. found a potential difference in efficacy between FTC and 3TC; however, the difference disappeared after adjusting for pill burden. Current evidence suggests that FTC and 3TC have equivalent efficacy and toxicity in ARV-naïve patients.<sup>3</sup>

### *Efficacy*

3TC has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data have demonstrated the safety of 3TC and have shown that this drug is associated with clinical improvement and virologic response. It is commonly used in children with HIV as a component of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone.<sup>4-12</sup> In one study that evaluated the efficacy of NRTI background components, the combination of 3TC plus abacavir (ABC) was superior to zidovudine (ZDV) plus 3TC or ZDV plus ABC in achieving long-term virologic efficacy.<sup>13</sup>



## *Pharmacokinetics in Infants*

Because of its safety profile and availability in a liquid formulation, 3TC has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.<sup>9</sup> A population pharmacokinetic (PK) analysis of infants who received 3TC affirms that adjusting the dose from 3TC 2 mg/kg to 3TC 4 mg/kg every 12 hours at age 4 weeks provides optimal 3TC exposure for infants with normal maturation of renal function.<sup>14</sup> For infants, the World Health Organization weight-band dosing (which is up to five times higher than the FDA-approved dose) results in greater plasma concentrations than the 3TC 2 mg/kg dose.<sup>15</sup> In HIV Prevention Trials Network (HPTN) 040, 3TC was administered as a component of a three-drug regimen to prevent perinatal transmission during the first 2 weeks of life. For 2 weeks, all infants weighing >2,000 g received 3TC 6 mg twice daily, and infants weighing ≤2,000 g received 3TC 4 mg twice daily. These doses resulted in 3TC exposure that was similar to the exposure seen in infants who received the standard twice-daily dosing schedule of 3TC 2 mg/kg per dose for neonates.<sup>16</sup>

## *Pharmacokinetics of Liquid Versus Tablet Preparations*

The PK of 3TC have been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects who received 3TC oral solution according to the recommended dose regimen achieved plasma concentrations of 3TC that were approximately 25% lower compared with those of adults with HIV who received the oral solution. Pediatric subjects who received 3TC tablets achieved plasma concentrations that were comparable to or slightly higher than those observed in adults who received tablets. In pediatric subjects, the relative bioavailability of 3TC oral solution is approximately 40% lower than the relative bioavailability of tablets that contain 3TC, despite no difference in the bioavailability of these two formulations among adults. The mechanisms for the diminished relative bioavailability of 3TC oral solution are unknown,<sup>17</sup> but results from a study in adults that compared the PK of 3TC oral solution administered either alone or with increasing concentrations of sorbitol indicate that sorbitol decreases the total exposure of 3TC oral solution.<sup>18</sup> Sorbitol is a component of several ARV solutions, including ABC, as well as common over-the-counter medications that may be used in infants and young children; this may explain the PK discrepancy between the oral solution and tablet formulations. Modeling of PK data in pediatric patients suggests that increasing the oral solution dose to 3TC 5 mg/kg per dose twice daily or 3TC 10 mg/kg per dose once daily (with a maximum of 3TC 300 mg administered daily) in children aged ≥3 months would provide exposures similar to those seen in adult patients who received tablet formulations. However, modeling was done with PK data derived from studies that did not use 3TC liquid formulation, and so modeling may not predict exposures for 3TC oral solution, especially when used with liquid ABC. The Panel **does not recommend** using a once-daily dose of 3TC until a child is aged ≥3 years. **After 3 years of age, switching to once-daily dosing with the liquid formulation could be considered when harmonizing with other ARV drugs administered once daily, such as ABC and dolutegravir (DTG).**

## *Dosing Considerations—Once-Daily Versus Twice-Daily Administration*

The standard adult dose for 3TC is 300 mg once daily, but data are lacking on once-daily administration of 3TC in children. Population PK data indicate that once-daily dosing of 3TC 8 mg/kg leads to area under the curve over 24 hours (AUC<sub>0–24h</sub>) values that are similar to those seen in patients taking 3TC 4 mg/kg twice daily, but minimum blood plasma concentration (C<sub>min</sub>) values are significantly lower and maximum blood plasma concentration (C<sub>max</sub>) values are significantly higher in children aged 1 year to 18 years.<sup>19</sup> Intensive PK of once-daily versus twice-daily dosing of

3TC were evaluated in children with HIV aged 2 to 13 years in the PENTA (Paediatric European Network for Treatment of AIDS) 13 trial<sup>4</sup> and in children aged 3 months to 36 months in the PENTA 15 trial.<sup>20</sup> Both the PENTA 13 and PENTA 15 trials used a crossover design with doses of 3TC 8 mg/kg once daily or 3TC 4 mg/kg twice daily. AUC<sub>0-24h</sub> and clearance values were similar between these two dosing schedules, and most children maintained an undetectable HIV RNA value after the switch. An ARROW (AntiRetroviral Research fOr Watoto) trial PK study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily 3TC also showed equivalent AUC<sub>0-24h</sub> and good clinical outcomes (defined by a low disease stage and a high CD4 T lymphocyte [CD4] cell count) after switching to once-daily 3TC. Median follow-up time during this study was 1.15 years.<sup>21</sup> The larger ARROW trial was a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of 3TC in >600 pediatric patients who had initiated therapy with twice-daily 3TC and who had been receiving therapy for ≥36 weeks. Median follow-up time during the study was 114 weeks. Rates of plasma HIV RNA suppression and adverse event profiles for once-daily 3TC were similar to (and statistically non-inferior to) those of twice-daily 3TC.<sup>22</sup>

All four of the studies discussed above enrolled patients who had low plasma HIV RNA or who were clinically stable on twice-daily 3TC before switching to once-daily dosing. Therefore, the Panel supports switching from twice-daily to once-daily dosing of 3TC in children aged ≥3 years who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 count. Clinicians should use a 10 mg/kg per dose of 3TC oral solution or a weight-based dose of 3TC tablets (neither exceeding 3TC 300 mg) as part of a once-daily regimen.<sup>23</sup> More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of 3TC can be used effectively as part of an initial ARV regimen in children.

3TC undergoes intracellular metabolism to reach its active form, 3TC triphosphate. In adolescents, the mean half-life of intracellular 3TC triphosphate (17.7 hours) is considerably longer than that of unphosphorylated 3TC in plasma (1.5–2 hours). Intracellular concentrations of 3TC triphosphate are equivalent whether 3TC is given once daily or twice daily in adults and adolescents. This supports a recommendation for once-daily 3TC dosing based on FDA recommendations.<sup>24,25</sup>

### ***Considerations for Use***

Weight-band dosing recommendations for 3TC have been developed for children weighing ≥3 kg and receiving either the 10-mg/mL oral solution or the 150-mg scored tablets.<sup>26-28</sup>

Recent data from the IMPAACT 2019 clinical trial of dispersible and immediate-release ABC/DTG/3TC tablets in children with HIV has confirmed the FDA-approved dosing in infants and children weighing 10 to <25 kg and confirmed newly proposed dosing of this FDC (three tablets once daily of ABC 60 mg, DTG 5 mg, and 3TC 30 mg dispersed in 15–20 mL of water) in infants weighing 6 to <10 kg. ABC/DTG/3TC dispersible FDC dosing was confirmed based on PK and safety data in each weight band at the originally selected dosing, which aligned with WHO weight-band dosing for the individual ARV agents. Follow-up through 24 weeks confirmed the safety, tolerability, and virological efficacy of both formulations. The dosing guidance for infants weighing 6 to <10 kg is awaiting regulatory approval.<sup>29</sup>

Both FTC and 3TC have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, see the [Hepatitis B Virus](#) section in the [Pediatric Opportunistic Infection Guidelines](#).

## Tenofovir Alafenamide (TAF, Vemlidy)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations							
<p>Tablet: 25 mg<sup>a</sup></p> <p><b>Fixed-Dose (FDC) Combination Tablets</b></p> <ul style="list-style-type: none"> <li>[Biktarvy] <ul style="list-style-type: none"> <li>Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg</li> <li>Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg</li> </ul> </li> <li>[Descovy] <ul style="list-style-type: none"> <li>Emtricitabine 200 mg/tenofovir alafenamide 25 mg</li> <li>Emtricitabine 120 mg/tenofovir alafenamide 15 mg</li> </ul> </li> <li>[Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> <li>[Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg</li> <li>[Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>							
Dosing Recommendations	Selected Adverse Events						
<p><b>[Biktarvy] Bictegravir (BIC)/Emtricitabine (FTC)/Tenofovir Alafenamide (TAF)</b></p> <p><i>Neonate or Child (Aged &lt;2 Years and Weighing &lt;14 kg) Dose</i></p> <ul style="list-style-type: none"> <li>No data are currently available on the appropriate dose of Biktarvy in children aged &lt;2 years and weighing &lt;14 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.</li> </ul> <p><i>Child (Aged ≥2 years), Adolescent, and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily, with or without food.</li> </ul> <table border="1"> <thead> <tr> <th>Body Weight</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>≥14 kg to &lt;25 kg</td> <td>BIC 30 mg/FTC 120 mg/TAF 15 mg</td> </tr> <tr> <td>≥25 kg</td> <td>BIC 50 mg/FTC 200 mg/TAF 25 mg</td> </tr> </tbody> </table>	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	<ul style="list-style-type: none"> <li>Asthenia, headache, diarrhea, nausea</li> <li>Increased serum lipids</li> </ul>
	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						
	Special Instructions						
	<ul style="list-style-type: none"> <li>Measure serum creatinine before starting a TAF-containing regimen.</li> <li>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.</li> <li>The FDA does not recommend using Genvoya with other ARV drugs, but this FDC tablet has been safely used with DRV.<sup>1</sup> Descovy can be safely used<sup>2</sup> with DRV or atazanavir in patients weighing ≥35 kg.</li> </ul>						

- The U.S. Food and Drug Administration (FDA) approved Biktarvy for use only in antiretroviral therapy (ART)–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 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 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 (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.

- Do not use** Genvoya with EVG, COBI, tenofovir disoproxil fumarate, FTC, 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 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)<sup>a</sup> 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<sup>3</sup> 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.

<p><i>Child and Adolescent (Weighing ≥25 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• 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 &lt;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.</li> </ul> <p><b>[Odefsey] FTC/Rilpivirine (RPV)/TAF</b></p> <p><i>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• 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 &lt;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.</li> </ul> <p><b>[Symtuza] Darunavir (DRV)/COBI/FTC/TAF</b></p> <p><i>Child and Adolescent (Weighing ≥40 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• 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 &lt;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.</li> </ul>	
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<sup>a</sup> 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.<sup>2</sup> 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.<sup>4</sup>

- Coadministration of TAF with rifamycins (rifabutin, rifampin, or rifapentine) **is not recommended**.<sup>3,5</sup>
- 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 bicitgravir (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 [Bicitgravir](#) 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<sup>6</sup> (see [Table 17h. 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  $\geq 14$  kg to  $< 25$  kg at a dose of FTC 120 mg/TAF 15 mg and for children who weigh  $\geq 25$  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  $\geq 35$  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<sup>7</sup> for use in children who weigh  $\geq 35$  kg. Genvoya, an FDC tablet that contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (EVG/c/FTC/TAF), is approved by the FDA for use in children who weigh  $\geq 25$  kg when used without other ARV drugs<sup>8</sup> (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<sup>9,10</sup> for use in children or adolescents with body weight  $\geq 14$  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  $\geq 25$  kg at a dose of BIC 50 mg/FTC 200 mg/TAF 25 mg.<sup>10,11-13</sup> Symtuza, an FDC tablet that contains DRV 800 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (DRV/c/FTC/TAF) is approved by the FDA<sup>10</sup> for use in children and adolescents who weigh  $\geq 40$  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](#) section of the [Pediatric Opportunistic Infection Guidelines](#). TAF alone (as Vemlidy) is approved by the FDA for use in people aged  $\geq 8$  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  $\geq 25$  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  $\geq 2$  years and weighing  $< 25$  kg and the other containing TAF 25 mg for people weighing  $\geq 25$  kg. COBI boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, in people weighing  $\geq 25$  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	18 years	N/A	Approved for HBV treatment only.
Descovy	FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	Use with an INSTI or NNRTI, but <b>not</b> 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	12 years	35 kg	<b>Generally not to be used with other ARV drugs.<sup>a</sup></b>
Genvoya	EVG/c/FTC/TAF	10 mg	N/A	25 kg	TAF dose is lower due to the COBI boosting. <b>Generally not to be used with other ARV drugs.<sup>a</sup></b>
Symtuza	DRV/c/FTC/TAF	10 mg	N/A	40 kg	TAF dose is lower due to the COBI boosting. <b>Generally not to be used with other ARV drugs.<sup>a</sup></b>
Biktarvy	BIC/FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	<b>Generally not to be used with other ARV drugs.<sup>a</sup></b>
	BIC/FTC/TAF	25 mg	N/A	≥25 kg	

<sup>a</sup> 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<sup>12,13</sup> and is so rapidly metabolized to TFV that TDF itself cannot be measured in blood (even when plasma is sampled within 5 minutes of administration).<sup>14</sup> 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.<sup>15,16</sup> Within the enterocyte and liver, TAF is not metabolized to TFV as quickly as TDF, so the plasma TFV concentration is much lower with administration of TAF than with TDF, and the main component in plasma is the prodrug itself, TAF.<sup>17</sup> Once inside the cell, TAF is hydrolyzed to TFV,<sup>18,19</sup> and then TFV-DP is produced by the same mechanism as for TDF. Relative to TDF, TAF more effectively delivers TFV to cells throughout the body.<sup>15</sup> 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.<sup>20</sup>

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.<sup>17,21</sup> 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).<sup>22</sup> High plasma TFV concentration also has been closely associated with both glomerular<sup>22-24</sup> and proximal tubular<sup>25</sup> 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 <sub>tau</sub> (ng·h/mL)	267.7 (26.7)	1,918.0 (39.4)
Plasma TFV C <sub>max</sub> (ng/mL)	15.7 (22.1)	252.1 (36.6)
Plasma TFV C <sub>tau</sub> (ng/mL)	9.2 (26.1)	38.7 (44.7)
PBMC TFV-DP AUC <sub>tau</sub> (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<sub>tau</sub> = area under the curve for the dosing interval (i.e., 24 hours); C<sub>max</sub> = peak concentration; C<sub>tau</sub> = 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<sup>26-29</sup>; with FTC and RPV<sup>30</sup>; with DRV, COBI, and FTC<sup>31-33</sup>; and when TAF and FTC are administered in combination with other ARV drugs.<sup>34</sup> 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<sup>35</sup> (-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.<sup>36-38</sup>

## Tenofovir Alafenamide Efficacy in Clinical Trials 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  $\geq 35$  kg and aged  $\geq 12$  years<sup>39</sup> and those weighing  $\geq 25$  kg and aged  $\geq 6$  years<sup>40</sup> (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<sup>9</sup> (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.<sup>41</sup>

## 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<sup>21</sup> to sevenfold higher than those generated with TDF at clinically meaningful doses.<sup>17,20,26</sup> Higher TFV-DP concentrations result in a stronger antiviral potency<sup>17</sup> and a higher barrier to resistance.<sup>42,43</sup> 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.<sup>39</sup>

### 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 <sub>max</sub> (90% CI) <sup>a</sup>	Mean Ratio of TAF AUC (90% CI) <sup>a</sup>
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 <sup>b</sup>	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)

Co-administered ARV	Dosage (Once Daily) (mg)	TAF Dosage (Once Daily) (mg)	N	Mean Ratio of TAF C <sub>max</sub> (90% CI) <sup>a</sup>	Mean Ratio of TAF AUC (90% CI) <sup>a</sup>
Efavirenz	600	40 <sup>b</sup>	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)

<sup>a</sup> Ratio represents concentrations of TAF plus the concomitant drug(s) divided by concentrations of TAF alone.

<sup>b</sup> Study was conducted with Descovy (emtricitabine [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<sub>max</sub> = maximum concentration; 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 <sup>a</sup>	TAF AUC Ratio TAF AUC of TAF-Containing Regimen/TAF AUC of Genvoya (Adult Exposure)	TFV AUC <sup>a</sup>	TFV AUC Ratio TFV AUC of TAF-Containing Regimen/TFV AUC of Stribild (Adult Exposure)
<b>Adult</b>				
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 <sup>b</sup>	196	0.93	259	0.06
DRV/c plus TAF 25 mg	239	1.1	935	0.21
<b>Pediatric</b>				
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

<sup>a</sup> AUC: ng·h/mL

<sup>b</sup> 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

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.<sup>44</sup> 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.<sup>45</sup> Hence, FTC/TAF 25 mg was initially recommended for approval instead of FTC/TAF 10 mg.<sup>45</sup> 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.”<sup>2</sup> 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]),<sup>2</sup> 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.<sup>8,46</sup>

### ***Drug Exposure and Safety: Aged 12 to 18 Years and Weighing $\geq 35$ kg***

A study of FTC/TAF in 18 children and adolescents (aged 12–18 years and weighing  $\geq 35$  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%).<sup>47</sup>

Studies of EVG/c/FTC/TAF in children aged 12 years to 18 years and weighing  $\geq 35$  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.<sup>39</sup> 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).<sup>2</sup>

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  $\geq 25$  kg and 50 children and adolescents aged 12 years to <18 years and weighing  $\geq 35$  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<sup>9</sup> 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  $\geq 25$  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.<sup>40,48</sup> This led to FDA approval of EVG/c/FTC/TAF for use in children aged  $\geq 6$  years and weighing  $\geq 25$  kg.<sup>8</sup> 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.<sup>49</sup>

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  $\geq 6$  years and weighing  $\geq 25$  kg when used in combination with other ARV drugs that do not include a boosted PI.<sup>2</sup>

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.<sup>50</sup> Therefore, FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing  $\geq 35$  kg (see [Table A](#) above).<sup>2</sup>



## ***Drug Exposure and Safety: Aged $\geq 2$ Years and Weighing $\geq 14$ kg to $< 25$ kg***

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF 15 mg were administered to children aged  $\geq 2$  years weighing 14 kg to  $< 25$  kg and who had viral loads  $< 50$  copies/mL on stable ART. At 24 weeks, the median change in CD4 T lymphocyte (CD4) cell count was  $-100$  cells/mm<sup>3</sup>, and the change in CD4 percentage was  $+0.5\%$ . HIV RNA at  $< 50$  copies/mL was maintained in 20 of the 22 participants at 24 weeks<sup>51</sup> (see the [Bictegravir](#) section for details). Safety and PK studies in children using TAF and FTC with atazanavir/cobicistat or DRV/c are ongoing.<sup>50</sup>

## ***Dosing: Crushing 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.<sup>52</sup> 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.<sup>53</sup> 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.<sup>54</sup> Based on an adult bioequivalence study, crushed BIC/FTC/TAF may lead to suboptimal FTC and TAF exposures.<sup>55</sup> Thus, crushed BIC/FTC/TAF **is not recommended** (see the [Bictegravir](#) section for details).

## **Toxicity**

### ***Bone***

TAF causes bone toxicity less frequently than TDF.<sup>26-28,31-34,56,57</sup> 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.<sup>26</sup> These differences were maintained until 96 weeks.<sup>29</sup> The clinical importance of these changes in BMD is unclear.

### ***Renal***

Studies in adolescents aged 12 to 17 years<sup>39</sup> and adults<sup>26-28,31,32,34</sup> show that TAF is less frequently associated with glomerular and renal tubular damage than TDF.<sup>58</sup> 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.<sup>26</sup> These differences persisted until 96 weeks of follow-up.<sup>29</sup> Safety of EVG/c/FTC/TAF has been demonstrated in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.<sup>59</sup> Postmarketing cases of renal impairment—including acute renal failure, proximal renal tubulopathy, and Fanconi syndrome—have been reported with TAF-containing products.<sup>2,3</sup> 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.<sup>60</sup> 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.<sup>32</sup> Monitoring serum lipids while the patient is taking TAF-containing FDC tablets is warranted, given these data (see [Table 17b. 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<sup>61-68</sup> (see [Table 17h. Lipodystrophies and Weight Gain](#) for details). Although weight gain at ART initiation might represent a “return to health,”<sup>63</sup> patients initiating treatment with TAF had larger increases in weight than those initiating treatment with TDF<sup>62,63</sup>; increases in weight and body mass index (BMI) have been observed in ARV switch studies, as well.<sup>64,67,69</sup> In adults, the effect may be greatest in Black females,<sup>63,67</sup> especially if administered in combination with INSTIs.<sup>63,65</sup> 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<sup>2</sup> at baseline.<sup>61</sup>



# Tenofovir Disoproxil Fumarate (TDF, Viread)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Oral Powder:</b> 40 mg per 1 g of oral powder (one level scoop, measured with supplied dosing scoop, equals 1 g oral powder)</p> <p><b>Tablets:</b> 150 mg, 200 mg, 250 mg, and 300 mg</p> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>• [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Truvada tablet] <ul style="list-style-type: none"> <li>○ Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>○ Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg</li> <li>○ Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg</li> <li>○ Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg</li> </ul> </li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonate and Infant Dose</b></p> <ul style="list-style-type: none"> <li>• Tenofovir disoproxil fumarate (TDF) has not been approved by the U.S. Food and Drug Administration or recommended for use in neonates or infants aged &lt;2 years.</li> </ul> <p><b>Child (Aged ≥2 Years to &lt;12 Years) and Weighing ≥10 kg Dose<sup>a</sup></b></p> <ul style="list-style-type: none"> <li>• TDF 8 mg/kg per dose once daily</li> </ul>	<ul style="list-style-type: none"> <li>• Asthenia, headache, diarrhea, nausea, vomiting, flatulence</li> <li>• Glomerular and proximal renal tubular dysfunction</li> <li>• Decreased bone mineral density<sup>a</sup></li> </ul>
	<ul style="list-style-type: none"> <li>• TDF oral powder formulation is available for patients who are unable to swallow tablets.</li> <li>• TDF oral powder should be measured only with the supplied dosing scoop: one level scoop = 1 g powder = TDF 40 mg.</li> </ul>

### TDF Oral Powder Dosing Table

Body Weight	TDF Oral Powder Once-Daily Scoops of Powder
10 kg to <12 kg	2 scoops (80 mg)
12 kg to <14 kg	2.5 scoops (100 mg)
14 kg to <17 kg	3 scoops (120 mg)
17 kg to <19 kg	3.5 scoops (140 mg)
19 kg to <22 kg	4 scoops (160 mg)
22 kg to <24 kg	4.5 scoops (180 mg)
24 kg to <27 kg	5 scoops (200 mg)
27 kg to <29 kg	5.5 scoops (220 mg)
29 kg to <32 kg	6 scoops (240 mg)
32 kg to <34 kg	6.5 scoops (260 mg)
34 kg to <35 kg	7 scoops (280 mg)
≥35 kg	7.5 scoops (300 mg)

### TDF Tablet Dosing Table

Body Weight	TDF Tablet Once Daily
17 kg to <22 kg	150 mg
22 kg to <28 kg	200 mg
28 kg to <35 kg	250 mg
≥35 kg	300 mg

#### Child and Adolescent (Weighing ≥35 kg)<sup>a</sup> and Adult Dose

- TDF 300 mg once daily

#### [Atripla and Generic] Efavirenz/Emtricitabine/TDF

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

- One tablet once daily
- Take on an empty stomach.

#### [Cimduo] Lamivudine/TDF

##### Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily

- Mix TDF oral powder with 2–4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with liquid. The powder may float on the top even after vigorous stirring.
- Although TDF can be administered without food, food requirements vary depending on the other ARV drugs contained in an FDC tablet. Food requirements are listed with dosing recommendations in [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)
- Measure serum creatinine and perform a urine dipstick test for protein and glucose before starting a TDF-containing regimen. Serum creatinine should be monitored, and urine should be tested for protein and glucose at intervals during continued therapy (see [Table 17i. Nephrotoxic Effects](#)). Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TDF.
- Tenofovir alafenamide (TAF) is associated with less bone and renal toxicity than TDF, but it has equal antiviral efficacy. **Do not use TAF and TDF together.** Consider switching from TDF to TAF in appropriate clinical settings.

### Metabolism/Elimination

#### TDF Dosing in Patients with Hepatic Impairment

- No change in TDF dosing is required for patients with hepatic impairment.
- Stribild **should not be used** in patients with severe hepatic impairment.
- Atripla, Symfi, and Symfi Lo should be used with caution in patients with hepatic impairment; Symfi and Symfi Lo are **not recommended** for use in moderate or severe hepatic impairment.

#### TDF Dosing in Patients with Renal Insufficiency

- The tenofovir metabolite of TDF is renally excreted.
- The dose of TDF should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult the manufacturer's prescribing information for directions on how to adjust the dose in accordance with CrCl.

**[Complera] Emtricitabine/Rilpivirine/TDF**

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

- One tablet once daily in antiretroviral therapy (ART)-naive adults with baseline HIV RNA ≤100,000 copies/mL. This dose of Complera also can be used in virologically suppressed (HIV RNA <50 copies/mL) adults who are currently on their first or second regimen and have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.
- Administer with a meal of ≥500 calories.

**[Delstrigo] Doravirine/Lamivudine/TDF**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose*

- One tablet once daily in ART-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and with no known mutations associated with resistance to the individual components of Delstrigo

**[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF**

*Adolescent (Weighing >35 kg with a Sexual Maturity Rating [SMR] of 4 or 5) and Adult Dose*

- One tablet once daily in ART-naive adults. This dose of Stribild 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 with no known mutations associated with resistance to the individual components of Stribild.
- Administer with food.

**[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

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

- One tablet once daily
- Take on an empty stomach.

**[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose*

- One tablet once daily
- Take on an empty stomach.

- The FDCs Atripla, Cimduo, Complera, Delstrigo, Symfi, Symfi Lo, or Temixys **should not be used** in patients with CrCl <50 mL/min or in patients who require dialysis.
- The FDC Truvada **should not be used** in patients with CrCl <30 mL/min or in patients who require dialysis.
- The FDC Stribild **should not be initiated** in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- **FTC and TDF require dosage adjustments in patients with these levels of renal impairment, and such adjustments cannot be achieved with an FDC tablet.**

- Symfi Lo has not been studied in children (SMR 1–3), and major inter-individual variability in efavirenz (EFV) plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs of 1–3 who weigh  $\geq 40$  kg. Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV suggest therapeutic drug monitoring when Symfi Lo is used in pediatric patients weighing  $\geq 40$  kg. See the [Efavirenz](#) section for more information.

**[Temixys] Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose*

- One tablet once daily

**[Truvada] Emtricitabine/TDF (FTC/TDF)**

*Child, Adolescent, and Adult Dose*

**Truvada Dosing Table**

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	One FTC 100 mg/ TDF 150 mg tablet
22 kg to <28 kg	One FTC 133 mg/ TDF 200 mg tablet
28 kg to <35 kg	One FTC 167 mg/ TDF 250 mg tablet
$\geq 35$ kg and adults	One FTC 200 mg/ TDF 300 mg tablet

<sup>a</sup> See the text for a discussion of the concerns about decreased bone mineral density in patients who are receiving TDF, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- **Metabolism:** Tenofovir disoproxil fumarate (TDF) is a substrate of the adenosine triphosphate–dependent transporters P-glycoprotein and breast cancer resistance protein. When TDF is coadministered with inhibitors of these transporters, an increase in TDF absorption may be observed, with the potential for enhanced TDF toxicity.<sup>1</sup>
- **Renal elimination:** Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir (TFV). Avoid frequent or long-term use of nonsteroidal anti-inflammatory drugs in patients who are taking TDF.

- *Other nucleoside reverse transcriptase inhibitors (NRTIs)*: Didanosine (ddI) serum concentrations increase when this drug is coadministered with TDF, and this combination **should not be used** because of the increased risk of ddI toxicity.
- *Protease inhibitors (PIs)*: Atazanavir (ATV) without ritonavir **should not be coadministered** with TDF, because TDF decreases ATV plasma concentrations. The combination of atazanavir/ritonavir, darunavir/ritonavir (DRV/r), and lopinavir/ritonavir increases plasma TFV concentrations and increases the risk of TDF-associated toxicity.<sup>1,2</sup>
- *Absorption*: Administering elvitegravir (EVG) concurrently with antacids and supplements that contain iron, calcium, aluminum, and/or magnesium lowers plasma concentrations of EVG. Similarly, dolutegravir (DTG) should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.<sup>3</sup> If using **Stribild**, see the [Elvitegravir](#) section of [Appendix A. Pediatric Antiretroviral Drug Information](#) for additional information.

## Major Toxicities

- *More common*: Nausea, diarrhea, vomiting, flatulence
- *Less common (more severe)*: TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF. Renal toxicity—including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calcinuria and decreased serum phosphate—has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

## 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*

TDF has been approved by the U.S. Food and Drug Administration (FDA) for use in children aged  $\geq 2$  years and weighing  $\geq 10$  kg when used as a component of antiretroviral therapy (ART). TDF is available as a component of fixed-dose combination tablets (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](#)).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is approved by the FDA for HBV treatment in children aged  $\geq 2$  years and weighing  $\geq 10$  kg. For a comprehensive review of this topic, see the [Hepatitis B Virus](#) section in the [Pediatric Opportunistic Infection Guidelines](#).

## ***Efficacy in Clinical Trials in Adults Compared with Children and Adolescents***

The standard adult dose that was approved by the FDA for adults and children aged  $\geq 12$  years and weighing  $\geq 35$  kg is TDF 300 mg once daily. For children aged 2 to 12 years, the FDA-approved dose is TDF 8 mg/kg per dose administered once daily, which closely approximates the dose of TDF 208 mg/m<sup>2</sup> per dose used in early studies in children.<sup>4</sup>

In adults, the recommended once-daily dose of TDF 300 mg is highly effective when used in combination with other antiretroviral (ARV) drugs.<sup>5-12</sup> The FDA approved Cimduo and Temixys (both of which contain lamivudine [3TC] 300 mg/TDF 300 mg) and Symfi (efavirenz [EFV] 600 mg/3TC 300 mg/TDF 300 mg) based on results of prior clinical trials.<sup>6,13</sup> FDA approval of Symfi Lo (EFV 400 mg/3TC 300 mg/TDF 300 mg) was based on a study that compared the use of EFV 400 mg with the use of EFV 600 mg, each administered with emtricitabine 200 mg and TDF 300 mg, in 630 ART-naive adults.<sup>14</sup> See the [Efavirenz](#) section for a detailed discussion of this study. In a large randomized controlled trial comparing second-line ART regimens, continuing TDF was superior to switching to zidovudine, when given in combination with 3TC and either DTG or DRV/r.<sup>15-17</sup>

In children, the published efficacy data for TDF-containing ARV combinations are mixed, but potency equal to that in adults has been seen in pediatric patients aged 3 to 18 years with susceptible virus. In children aged 2 years to  $< 12$  years, TDF 8 mg/kg per dose once daily was non-inferior to twice-daily zidovudine-containing ART or stavudine-containing ART over 48 weeks of randomized treatment.<sup>18,19</sup> Virologic success is lower in treatment-experienced patients with extensive multiclass drug resistance.<sup>20-22</sup> In an analysis of genotypic resistance testing performed on 650 unique patients at a single laboratory in the Republic of South Africa, predicted intermediate or high-level resistance to TDF was lower for children experiencing virologic failure while on abacavir (ABC)-containing (8.5%) and zidovudine-containing (9.4%) regimens than those experiencing virologic failure while on a TDF-containing regimen (24.6%). Clinical data are lacking in children on the efficacy of switching from a failing regimen containing these NRTIs to a regimen containing TDF.<sup>23</sup>

## **Pharmacokinetics**

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

Virologic suppression is most closely related to intracellular tenofovir diphosphate (TFV-DP) concentrations and, for TDF, intracellular TFV-DP is linked to plasma TFV concentration.<sup>24</sup> A modeling study suggests that children and adolescents who are treated with TDF may have higher intracellular TFV-DP concentrations than adults,<sup>25</sup> even though plasma TFV concentrations are lower in children and adolescents, because weight-adjusted renal clearance of TFV is higher in children than in adults.<sup>4,26,27</sup>

## **Formulations**

### ***Special Considerations***

The taste-masked granules that make up the TDF oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed with a vehicle, TDF should be administered promptly because its taste becomes bitter when it is allowed to sit for too long.

## Toxicity

### ***Bone Toxicity***

TDF administration is associated with decreased BMD in both adults<sup>28,29</sup> and children.<sup>19,30-32</sup> When treated with TDF, younger children with sexual maturity ratings (SMRs) of 1 and 2 may be at a higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMRs  $\geq 3$ ).<sup>26</sup> Discontinuation of TDF results in partial or complete recovery of BMD.<sup>30,33</sup>

In the study that led to FDA approval of TDF in adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg, 6 of 33 participants (18%) in the TDF arm experienced a  $>4\%$  decline in absolute lumbar spine BMD in 48 weeks, whereas only 1 of 33 participants (3%) in the placebo arm experienced this decline.<sup>20</sup>

TDF administration disrupts vitamin D metabolism,<sup>34,35</sup> and the decrease in BMD associated with TDF initiation was attenuated in adults with coadministration of high doses of vitamin D3 (4,000 IU daily) and calcium carbonate (1,000 mg daily) for the first 48 weeks of TDF treatment.<sup>36</sup> During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone levels and increased lumbar spine BMD compared with study participants who were not treated with high doses of vitamin D3.<sup>34,37</sup> The serum 25-hydroxy vitamin D concentration was 37 ng/mL in the group with improved BMD. Similar improvements in BMD were seen in youth with HIV who were treated with an ARV regimen that included TDF and who received vitamin D3 2,000 IU or 4,000 IU daily.<sup>38</sup> Measurement of plasma vitamin D concentration is recommended for patients who are being treated with an ARV regimen that includes TDF, and vitamin D supplementation is recommended for those with vitamin D deficiency (see [Table 17j. Osteopenia and Osteoporosis](#)).

High concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.<sup>39</sup> Plasma TFV concentrations are higher when TDF is coadministered with boosted PIs.<sup>1</sup> Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, has less effect on parathyroid hormone levels<sup>40</sup> and causes less decline in BMD than TDF. See the [Tenofovir Alafenamide](#) section for more information. Consider switching from TDF to TAF or avoiding coadministration of TDF with boosted PIs in patients for whom loss of BMD is a concern.

### ***Monitoring Potential Bone Toxicity***

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does **not recommend** routine dual-energy X-ray absorptiometry monitoring for children or adolescents who are being treated with TDF (see [Table 17j. Osteopenia and Osteoporosis](#)).

TDF has been shown to be effective, and it can be administered once daily; however, the use of TDF has been associated with a risk of BMD loss. Because childhood and early adolescence are important periods of rapid bone accrual, and because children with perinatally acquired HIV are at risk for low peak bone mass,<sup>41,42</sup> the Panel favors the use of ABC or TAF over TDF in children with SMRs 1 to 3.



## ***Renal Toxicity***

New-onset renal impairment and worsening renal impairment have been reported in adults<sup>43</sup> and children<sup>44,45</sup> receiving TDF. In one study, renal toxicity led to the discontinuation of TDF in 6 of 159 (3.7%) children with HIV who were treated with TDF.<sup>22</sup> Although TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.<sup>43,44</sup> Irreversible renal failure is quite rare, but cases have been reported.<sup>46</sup>

The main target of TDF nephrotoxicity is the renal proximal tubule.<sup>44</sup> Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.<sup>47,48</sup>

Subclinical renal tubular damage is more common than clinically apparent renal tubular injury. Increased urinary beta-2 microglobulin was identified in 12 of 44 children (27%) who were treated with TDF and in 2 of 48 children (4%) who were not treated with TDF.<sup>49</sup> The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.<sup>50,51</sup> Of 89 participants aged 2 to 12 years who received TDF in Gilead Study 352 (where participants had a median drug exposure of 104 weeks), four participants were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.<sup>18</sup> In adults, renal dysfunction is more common when TDF is used in patients with older age or a pre-existing renal disease<sup>52</sup>; in children, renal dysfunction may be more common when TDF is used with boosted PIs than with non-nucleoside reverse transcriptase inhibitors.<sup>53</sup>

Plasma TFV is the TDF metabolite most closely associated with both glomerular<sup>39,54</sup> and proximal tubular<sup>55</sup> toxicity. As previously noted, plasma TFV concentrations are higher when TDF is coadministered with boosted PIs.<sup>1</sup> TAF, which generates lower plasma TFV concentrations than TDF, is associated with a lower risk of renal toxicity than TDF<sup>56</sup> (see [Tenofovir Alafenamide](#)).

## ***Monitoring Potential Renal Toxicity***

Because TDF has the potential to decrease creatinine clearance and cause renal tubular dysfunction, the Panel recommends measuring serum creatinine and using a urine dipstick to check protein and glucose concentration before initiating TDF. It is unclear how often creatinine and renal tubular function (urine protein and glucose) should be monitored in asymptomatic patients. Many Panel members monitor creatinine with other blood tests every 3 to 4 months and perform urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and in the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases the concentration of albumin in urine, and proximal renal tubular damage increases the concentration of low-molecular-weight proteins like beta-2 microglobulin in urine, dipstick urinalysis (which primarily measures urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measuring urine albumin and urine protein and calculating the ratio of urine albumin to urine protein can be helpful in identifying the non-albumin proteinuria that is seen in TDF-associated nephrotoxicity.<sup>57,58</sup> Although these more complex and expensive tests may be used in research settings, in clinical practice, using a renal dipstick to identify normoglycemic glycosuria and proteinuria is the easiest way to detect renal damage.

## Zidovudine (ZDV, Retrovir)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations					
<p><b>Syrup:</b> 10 mg/mL</p> <p><b>Capsule:</b> 100 mg</p> <p><b>Concentrate for Injection or Intravenous Infusion:</b> 10 mg/mL (Retrovir)</p> <p><b>Generic Formulations</b></p> <ul style="list-style-type: none"> <li>• 100-mg capsule</li> <li>• 10-mg/mL syrup</li> <li>• 300-mg tablet</li> </ul> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>• [Generic] Lamivudine 150 mg/zidovudine 300 mg (scored)</li> <li>• [Generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg</li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>					
Dosing Recommendations	Selected Adverse Events				
<p><b>Note:</b> Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection</a> and <a href="#">Table 12</a> for information about using ZDV to prevent perinatal transmission.</p> <p><b>Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth<sup>a</sup></b></p> <table border="1"> <thead> <tr> <th>Gestational Age at Birth</th> <th>Oral ZDV Dose</th> </tr> </thead> <tbody> <tr> <td>≥35 Weeks</td> <td> <p><b>Birth to Age 4 Weeks</b></p> <ul style="list-style-type: none"> <li>• ZDV 4 mg/kg twice daily; <i>or</i></li> <li>• Alternative simplified weight-band dosing</li> </ul> <p><b>Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth</b></p> <p><b>Note:</b> The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.</p> </td> </tr> </tbody> </table>	Gestational Age at Birth	Oral ZDV Dose	≥35 Weeks	<p><b>Birth to Age 4 Weeks</b></p> <ul style="list-style-type: none"> <li>• ZDV 4 mg/kg twice daily; <i>or</i></li> <li>• Alternative simplified weight-band dosing</li> </ul> <p><b>Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth</b></p> <p><b>Note:</b> The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.</p>	<ul style="list-style-type: none"> <li>• Bone marrow suppression leading to anemia and neutropenia, macrocytosis with or without anemia</li> <li>• Nausea, vomiting, headache, insomnia, asthenia</li> <li>• Lactic acidosis/severe hepatomegaly with hepatic steatosis</li> <li>• Lipodystrophy and lipoatrophy</li> <li>• Myopathy (associated with prolonged use of ZDV) and myositis</li> </ul>
Gestational Age at Birth	Oral ZDV Dose				
≥35 Weeks	<p><b>Birth to Age 4 Weeks</b></p> <ul style="list-style-type: none"> <li>• ZDV 4 mg/kg twice daily; <i>or</i></li> <li>• Alternative simplified weight-band dosing</li> </ul> <p><b>Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth</b></p> <p><b>Note:</b> The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.</p>				
	Special Instructions				
	<ul style="list-style-type: none"> <li>• Give ZDV without regard to food.</li> <li>• If substantial granulocytopenia or anemia develops in patients who are receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.</li> </ul>				

	<table border="1"> <thead> <tr> <th>Weight Band</th> <th>Twice-Daily Volume of ZDV 10 mg/mL Syrup</th> </tr> </thead> <tbody> <tr> <td>2 kg to &lt;3 kg</td> <td>1 mL</td> </tr> <tr> <td>3 kg to &lt;4 kg</td> <td>1.5 mL</td> </tr> <tr> <td>4 kg to &lt;5 kg</td> <td>2 mL</td> </tr> </tbody> </table> <p><b>Aged &gt;4 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 12 mg/kg twice daily</li> </ul>	Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup	2 kg to <3 kg	1 mL	3 kg to <4 kg	1.5 mL	4 kg to <5 kg	2 mL	<ul style="list-style-type: none"> <li>Screen patients for hepatitis B virus (HBV) infection before using FDC products that contain lamivudine (3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking 3TC.</li> </ul> <p style="text-align: center;"><b>Metabolism/Elimination</b></p> <ul style="list-style-type: none"> <li>ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.</li> <li>ZDV is phosphorylated intracellularly to active ZDV triphosphate.</li> </ul> <p><b>ZDV Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>The dose of ZDV may need to be reduced in patients with hepatic impairment.</li> <li>Do not use FDC products in patients who have impaired hepatic function.</li> </ul> <p><b>ZDV Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>A dose adjustment is required for ZDV in patients with renal insufficiency.</li> <li>Do not use FDC products in patients with creatinine clearance &lt;50 mL/min and patients who are on hemodialysis.</li> </ul>
Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup									
2 kg to <3 kg	1 mL									
3 kg to <4 kg	1.5 mL									
4 kg to <5 kg	2 mL									
≥30 Weeks to <35 Weeks	<p><b>Birth to Age 2 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 2 mg/kg twice daily</li> </ul> <p><b>Aged 2 Weeks to 6 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;6 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 12 mg/kg twice daily</li> </ul>									
<30 Weeks	<p><b>Birth to Age 4 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 2 mg/kg twice daily</li> </ul> <p><b>Aged 4 Weeks to 8 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;8 Weeks</b></p> <ul style="list-style-type: none"> <li>ZDV 12 mg/kg twice daily</li> </ul>									

**Note:** For infants who are unable to tolerate oral agents, the intravenous dose should be 75% of the oral dose, but the dosing interval should remain the same.

**Infant (Aged ≥35 Weeks Post-conception and ≥4 Weeks Post-delivery, Weighing ≥4 kg) and Child Dose Weight-Based Dosing for ZDV**

Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

**Alternative Body Surface Area Dosing**

*Oral*

- ZDV 180–240 mg per m<sup>2</sup> of body surface area every 12 hours

**Child and Adolescent (Weighing ≥30 kg) and Adult Dose**

- ZDV 300 mg twice daily

<p><b>Lamivudine (3TC)/ZDV</b>  <i>Child and Adolescent (Weighing ≥30 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• One tablet twice daily</li> </ul> <p><b>Abacavir/3TC/ZDV</b>  <i>Child and Adolescent (Weighing ≥30 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• One tablet twice daily</li> </ul>	
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<sup>a</sup> For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with postgestational age and clinical status of the infant.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Bone marrow suppressive/cytotoxic agents, including ganciclovir, valganciclovir, interferon alfa, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine (ZDV).
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues—such as ribavirin—antagonize *in vitro* antiviral activity of ZDV.
- *Doxorubicin:* Simultaneous use of doxorubicin and ZDV **should be avoided**. Doxorubicin may inhibit the phosphorylation of ZDV to its active form.

## Major Toxicities

- *More common:* Hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants who are receiving both lamivudine (3TC) and ZDV than in infants who are receiving only ZDV.<sup>1</sup>
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution has been observed in patients receiving antiretroviral (ARV) medications.
- *Rare:* Possible increased risk of cardiomyopathy.<sup>2-4</sup>

## Resistance

The International Antiviral Society–USA maintains a list of [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

ZDV is frequently included as a component of the nucleoside reverse transcriptase inhibitor (NRTI) backbone for antiretroviral therapy (ART), and it has been studied in children in combination with

other NRTIs, including abacavir (ABC) and 3TC.<sup>5-8</sup> Pediatric experience with ZDV both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of ZDV leads many experts to favor the use of ABC or tenofovir alafenamide in cases where the patient's age and the results of viral resistance testing do not restrict the use of these drugs.

### ***Efficacy in Clinical Trials***

The combination of ZDV and 3TC has been extensively studied in children and has been a part of ARV regimens in many trials. The safety and efficacy of ZDV plus 3TC were compared to the safety and efficacy of ABC plus 3TC and stavudine (d4T) plus 3TC in children aged <5 years in the CHAPAS-3 (Children with HIV in Africa Pharmacokinetics and Adherence of Simple antiretroviral regimens) study. All regimens also included either nevirapine (NVP) or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.<sup>9</sup> A number of studies have evaluated the efficacy and toxicity of different dual-NRTI backbones used as part of combination ART.<sup>10-12</sup>

### ***Infants with Perinatal HIV Exposure***

The Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial<sup>13</sup> demonstrated that administering ZDV to pregnant women and their infants could reduce the risk of perinatal HIV transmission by nearly 70%. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) for further discussion on using ZDV to prevent perinatal transmission of HIV. A dose of approximately ZDV 4 mg/kg of body weight every 12 hours is recommended for prevention of perinatal HIV transmission in neonates and infants with gestational ages  $\geq 35$  weeks. Infants who have been exposed to HIV but are uninfected should continue on the prophylactic dose for 2 to 6 weeks, depending on their gestational age at time of delivery and the risk assessment for perinatal transmission.

Simplified, alternative weight-band dosing has also been developed, and the rationale for these doses is based on the intracellular metabolism of ZDV (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of ZDV to active ZDV triphosphate is the limited amount of thymidylate kinase. Increasing the dose of ZDV will lead to increased ZDV plasma concentrations and increased intracellular concentrations of ZDV monophosphate, but not ZDV diphosphate or ZDV triphosphate.

In 31 infants who received ZDV to prevent perinatal transmission, levels of intracellular ZDV metabolites were measured after delivery. Plasma ZDV and intracellular ZDV monophosphate decreased by roughly 50% between postdelivery Day 1 and Day 28, whereas ZDV diphosphate and ZDV triphosphate remained low throughout the sampling period.<sup>14</sup> ZDV dose is poorly correlated with the active form of ZDV that is found intracellularly. Because of this, a simplified weight-band dosing approach can be used for the first 4 weeks of life in infants with gestational ages  $\geq 35$  weeks (see the dosing table above). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during ZDV use in the first 4 weeks of life and will make it easier for caregivers to administer ZDV oral syrup to their infants. The changes in weight and the small differences in ZDV dose will have minor effects on the intracellular concentrations of ZDV triphosphate.

## ***Infants with HIV Infection***

The Early Infant Treatment Study in Botswana evaluated the safety and efficacy of initiation of ART in the first week of life. Forty infants who tested positive for HIV within 96 hours of birth were started on ZDV, 3TC, and NVP with successful transition to lopinavir/ritonavir (LPV/r) at 2 to 5 weeks after delivery. Early treatment was found to be safe and effective, with most infants achieving and maintaining viral suppression by 24 weeks of age.<sup>15</sup>

For full-term neonates who receive an HIV diagnosis during the first days to weeks of life, the ZDV dose should be increased to the continuation dose at age 4 weeks (see the dosing table above). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 to 6 weeks of life in full-term neonates. This increase in metabolizing enzyme activity leads to an increased clearance of plasma ZDV, and the dose of ZDV should be adjusted when ZDV is used to treat HIV after the first 4 weeks in full-term infants.

For premature infants who receive an HIV diagnosis, the time to increase the ZDV dose from the initial dose varies with postgestational age and the clinical status of the neonate. On the basis of population pharmacokinetic (PK) modeling and simulations and data from studies that have evaluated ZDV PKs in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following:

- For infants with HIV born at  $\geq 30$  weeks to  $< 35$  weeks, switch to a dose of ZDV 12 mg/kg twice daily at a postgestational age of 6 to 8 weeks.
- For infants born at  $< 30$  weeks, switch to ZDV 12 mg/kg twice daily at a postgestational age of 8 to 10 weeks.<sup>16</sup>

Clinicians should perform a careful clinical assessment of the infant, evaluate hepatic and renal function, and review concomitant medications before increasing the ZDV dose to the dose recommended for full-term infants.

## **Pharmacokinetics**

ZDV undergoes intracellular metabolism to achieve its active form, ZDV triphosphate. Phosphorylation requires multiple steps: ZDV is phosphorylated by thymidine kinase to ZDV monophosphate, ZDV monophosphate is phosphorylated by thymidylate kinase to ZDV diphosphate, and ZDV diphosphate is phosphorylated by nucleoside diphosphate kinase to ZDV triphosphate. Overall, ZDV PK in pediatric patients aged  $> 3$  months are like those seen in adults. Although the mean half-life of intracellular ZDV triphosphate (9.1 hours) is considerably longer than that of unmetabolized ZDV in plasma (1.5 hours), once-daily ZDV dosing is not recommended because of the low intracellular ZDV triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.<sup>17</sup> PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of ZDV compared with the clearance observed in term newborns of similar postnatal ages.<sup>6</sup> ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid–to–plasma concentration ratio is 0.68), and ZDV has been used in children with HIV-related CNS disease.<sup>8</sup>

PK and safety of ZDV, 3TC, and LPV/r in children with HIV and severe acute malnutrition (SAM) was studied in International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPACT) P1092.<sup>18</sup> Steady-state PK, safety, and tolerability was compared in children with HIV with and



without SAM. Overall safety and tolerability did not differ between the two cohorts, and similar area-under-the-curve values for ZDV, 3TC, and LPV/r were observed in these children who were dosed according to World Health Organization weight-band dosing recommendations.<sup>18</sup>

The PK of intravenous ZDV in a premature neonate with gestational age of 32 weeks on extra corporal membrane oxygenation (ECMO) has been reported in a single case report. Based on measurements of ZDV plasma concentrations during and after ECMO, the authors concluded that ECMO did not have an impact on ZDV PK and that standard intravenous dosing of ZDV can be used in preterm neonates.<sup>19</sup>

## Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area-under-the-curve values for ZDV.<sup>5,6,20</sup> A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.<sup>21</sup> In this study, 137 infants received ZDV for 2 weeks and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ( $P < 0.001$ ) and age 3 months ( $P < 0.001$ ).<sup>21</sup> For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation. A recent study conducted in Thailand evaluated the safety of triple ARV neonatal presumptive therapy with ZDV/3TC/NVP for 6 weeks in infants at high risk of acquisition of HIV compared with 4 weeks of monotherapy with ZDV in infants considered at low risk. No significant differences were observed in the incidence of neutropenia, hepatotoxicity, or severe anemia between the triple ARV and the ZDV monotherapy groups.<sup>22</sup>

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naïve Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.<sup>23</sup> In a retrospective study conducted in Ethiopia, an evaluation of predictors of anemia among children on ART<sup>24</sup> was conducted from 2007 to 2017. Study participants receiving ZDV-containing regimens were four times more likely to develop anemia than those children receiving ABC-containing regimens. Other predictors of anemia in addition to ZDV in this patient population included tuberculosis, severe immunosuppression, and undernutrition.

ZDV is associated with greater mitochondrial toxicity than ABC and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than d4T.<sup>25,26</sup>

Although the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the use of ART became routine, the use of a regimen that contains ZDV may increase the risk.<sup>24</sup> Analysis of data from a U.S.-based multicenter prospective cohort study (PACTG 219/219C) found that ongoing ZDV exposure was independently associated with a higher rate of cardiomyopathy.<sup>2</sup> As part of the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, echocardiogram measurements were collected between 2008 and 2010 in 325



youth aged 7 to 16 years with perinatally acquired HIV infection. An association between ZDV use and increased end-systolic wall stress was observed in this study. The investigators speculate that alterations in cardiac structure in these children could progress to symptomatic cardiomyopathy later in life.<sup>3</sup> A large cohort study to evaluate the prevalence of cardiac dysfunction in children and young adults <26 years of age was conducted in Kenya.<sup>4</sup> Approximately 28% of participants were found to have evidence of early cardiac dysfunction. Left ventricular ejection fraction negatively correlated with prior ZDV exposure, detectable HIV RNA, and elevated interleukin-6 concentrations.<sup>4</sup>

# Appendix A: Pediatric Antiretroviral Drug Information

## Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant)

## Doravirine (DOR, Pifeltro)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations		
<p>Tablet: 100 mg</p> <p><b>Fixed-Dose Combination (FDC) Tablet</b></p> <ul style="list-style-type: none"> <li>[Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> </ul> <p>When using FDC tablets, refer to other sections of the <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>		
Dosing Recommendations	Selected Adverse Events	
<p><b>Child and Adolescent (Weighing <math>\geq 35</math> kg) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>DOR 100 mg once daily in antiretroviral (ARV)-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA &lt;50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR</li> </ul> <p><b>[Delstrigo] DOR/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)</b></p> <p><i>Child and Adolescent (Weighing <math>\geq 35</math> kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily in ARV-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA &lt;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 Delstrigo</li> </ul>	<ul style="list-style-type: none"> <li>Nausea</li> <li>Abdominal pain</li> <li>Diarrhea</li> <li>Abnormal dreams</li> <li>Insomnia, somnolence</li> </ul>	
	Special Instructions	<ul style="list-style-type: none"> <li>DOR can be taken with or without food.</li> <li>Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains 3TC and TDF. Severe acute exacerbation of HBV can occur when 3TC or TDF are discontinued; therefore, hepatic function and HBV viral load should be monitored for several months after halting therapy with 3TC or TDF.</li> </ul>
	Metabolism/Elimination	<ul style="list-style-type: none"> <li>DOR is metabolized by the enzyme cytochrome P450 3A.</li> <li>DOR has multiple interactions with several drugs (see Drug Interactions section below).</li> <li>When DOR is coadministered with rifabutin, the dose should be increased from DOR 100 mg once daily to DOR 100 mg twice daily. When DOR/3TC/TDF (Delstrigo) is coadministered with rifabutin, an additional 100-mg dose of freestanding DOR needs to be administered approximately 12 hours later. (See Drug Interactions below.)</li> </ul>

	<p><b>DOR Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>• Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment.</li> </ul> <p><b>DOR Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• Dose adjustment is not required when using DOR in patients with mild, moderate, or severe renal impairment. DOR use has not been studied in patients with end-stage renal disease or in patients on dialysis.</li> <li>• DOR administered with 3TC and TDF as components of Delstrigo is <b>not recommended</b> in patients with estimated creatinine clearance &lt;50 mL/min.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Doravirine (DOR) is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in DOR plasma concentrations and potential decreases in efficacy, which can lead to the development of resistance. Before DOR is administered, a patient’s medication profile should be reviewed carefully for potential drug interactions with DOR.<sup>1,2</sup>
- In a Phase 1 trial (described below under Efficacy in Clinical Trials), DOR plasma exposure transiently decreased by 62% when DOR was started immediately after stopping EFV. A *post hoc* analysis of the Phase 3 DRIVE-SHIFT study (described below under Efficacy in Clinical Trials), however, showed that at Week 4, DOR plasma levels in patients who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in patients who switched from a protease inhibitor (PI)-based regimen to a DOR-based regimen (all of the regimens in the study used a backbone of lamivudine [3TC] plus tenofovir disoproxil fumarate [TDF]).<sup>3</sup> A similar effect of prior EFV-based ART on the pharmacokinetics (PK) of DOR was demonstrated in IMPAACT 2014 (described below under Efficacy in Clinical Trials) among adolescents weighing  $\geq 45$  kg who switched from EFV-based ART to DOR-based ART with 3TC/TDF.<sup>4</sup>
- DOR **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John’s wort.<sup>5,6</sup>
- Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours after a fixed-dose combination of DOR/3TC/TDF or an increase of the DOR dose to 100 mg twice daily.<sup>2,5,6</sup>

## Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.

- *Less common (more severe)*: Neuropsychiatric adverse events (AEs), including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

## Resistance

The International Antiviral Society–USA maintains a list of updated [drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

DOR is expected to have activity against HIV with isolated non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance that is associated with mutations at positions 103, 181, or 190. Some single mutations and combinations of viral mutations, however, have been shown to significantly decrease susceptibility to DOR. Specifically, clinical HIV isolates containing the Y188L mutation alone or in combinations with K103N or V106I, combinations of V106A with G190A and F227L, or combinations of E138K with Y181C and M230L have shown  $\geq 100$ -fold reduction in susceptibility to DOR.<sup>5,6</sup> In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of DOR.

## Pediatric Use

### *Approval*

DOR is approved by the U.S. Food and Drug Administration (FDA) for use in children and adolescents weighing  $\geq 35$  kg.<sup>5,6</sup> [IMPAACT 2014](#), a Phase 1/2 study (described below under Efficacy in Clinical Trials) evaluated the PK, safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV.<sup>4</sup>

### *Efficacy in Clinical Trials*

The efficacy of DOR was evaluated using data from four randomized adult clinical trials. The first study was a Phase 2b dose-selection, double-blind trial that enrolled treatment-naive adults with HIV.<sup>7</sup> The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials ([DRIVE-FORWARD](#) and [DRIVE-AHEAD](#)) in treatment-naive adults<sup>8-11</sup> and one open-label, active-controlled, randomized noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy ([DRIVE-SHIFT](#)).<sup>12</sup>

The dose-selection trial enrolled treatment-naive adults stratified by HIV RNA level at screening ( $\leq 100,000$  copies/mL or  $> 100,000$  copies/mL) and randomized participants to receive one of four different doses (25 mg, 50 mg, 100 mg, or 200 mg) of once-daily DOR or EFV 600 mg with open-label emtricitabine (FTC) 200 mg/TDF 300 mg. After dose selection at Week 24, all participants were switched to DOR 100 mg and, with additional enrollment, 216 participants were randomized to receive once-daily DOR 100 mg (n = 108) or EFV 600 mg (n = 108) for 96 weeks with FTC/TDF. At Week 24, 72.9% of participants on DOR 100 mg and 73.1% of participants on EFV 600 mg had HIV RNA  $< 40$  copies/mL.<sup>7</sup>

In the DRIVE-FORWARD trial, adult subjects received either DOR 100 mg (n = 383) or darunavir 800 mg/ritonavir 100 mg (DRV/r) (n = 383) once daily, each in combination with FTC/TDF or abacavir/3TC.<sup>8</sup> In the DRIVE-AHEAD trial, adult subjects received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily.<sup>9</sup> An integrated efficacy analysis

from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of patients who were treated with the DOR-based regimen achieved HIV RNA <50 copies/mL, compared with 79.9% of patients who were treated with the DRV/r-based regimen and 80.8% of patients who were treated with EFV/FTC/TDF. Results were similar across different baseline viral loads, genders, races, and HIV-1 subtypes.<sup>9</sup> In a longer-term analysis, at Week 96 in the DRIVE-AHEAD trial, among 728 randomized participants, 77.5% of those treated with DOR/3TC/TDF achieved HIV RNA <50 copies/mL, compared with 73.6% in participants treated with EFV/FTC/TDF. No additional resistance to DOR was observed between Weeks 48 and 96.<sup>11</sup> At Week 96 in the DRIVE-FORWARD trial, 277 (95%) of 292 participants who remained on DOR maintained viral suppression (i.e., 73% of the overall 383 participants), whereas 248 (91%) of 273 participants who remained on DRV/r maintained viral suppression (i.e., 66% of the overall 383 participants).<sup>10</sup>

In the DRIVE-SHIFT study, adult subjects with HIV who were virologically suppressed for  $\geq 6$  months on two nucleoside reverse transcriptase inhibitors plus a boosted PI, boosted elvitegravir, or an NNRTI were randomized to switch to a once-daily, single-tablet regimen of DOR 100 mg/3TC 300 mg/TDF 300 mg or continue their current therapy (baseline regimen). At Week 24, 93.7% on DOR/3TC/TDF versus 94.6% on baseline regimen had HIV-1 RNA <50 copies/mL (difference  $-0.9$  [ $-4.7$  to  $3.0$ ]). At Week 48, 90.8% on DOR/3TC/TDF had HIV-1 RNA <50 copies/mL, demonstrating noninferiority versus baseline regimen at Week 24 (difference  $-3.8$  [ $-7.9$  to  $0.3$ ]).<sup>12</sup> Participants were switched on Day 1 (immediate-switch group [ISG];  $n = 447$ ) or at Week 24 (delayed-switch group [DSG];  $n = 209$ ). Long-term efficacy in the extension arm at Week 144 showed virologic suppression (HIV RNA <50 copies/mL) in 80.1% of ISG (351 of 438) and 83.7% of DSG (175 of 209) in FDA snapshot (intent-to-treat) analysis.<sup>13</sup>

IMPAACT 2014 study data in antiretroviral (ARV)-naive or ARV-experienced virologically suppressed adolescents suggest favorable antiviral effect comparable to adult data.<sup>4</sup> A total of 45 participants, 43 virologically suppressed (50% on EFV-based ART) and 2 ARV-naive adolescents with mean age 15 years (12–17 years), were treated with DOR/3TC/TDF. At Week 24, 42 of 45 (93.3%; 95% confidence interval [CI], 81.7–98.6) achieved or maintained HIV-1 RNA <40 copies/mL in FDA snapshot (intent-to-treat) analysis, while 42 of 43 (97.7%; 95% CI, 87.7–99.9) achieved or maintained HIV-1 RNA <40 copies/mL in observed failure (on-treatment) analysis.<sup>4</sup>

## Pharmacokinetics

The PK of DOR have been evaluated in treatment-naive adults aged  $\geq 18$  years and both treatment-naive and treatment-experienced adolescents. A Phase 2 trial evaluated DOR across a dose range of 0.25 times to 2 times the recommended dose in treatment-naive participants with HIV who also received FTC/TDF. No exposure-response relationship for efficacy was reported for DOR.<sup>9</sup>

## Toxicity

In trials that compared DOR-based regimens and EFV-based regimens, central nervous system (CNS) AEs (dizziness, sleep disorder and disturbances, and altered sensorium) occurred less frequently among the patients who received DOR than among those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens, compared with 47.2% of patients on EFV-based regimens at Week 24.<sup>7</sup> In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of patients on DOR-based regimens

experienced CNS AEs at Week 48, compared with 55.9% of patients on EFV-based regimens.<sup>9,14</sup> Neither DRIVE-FORWARD nor DRIVE-AHEAD included an integrase strand transfer inhibitor-based regimen as an active control. Fewer participants who received DOR-based regimens experienced diarrhea than those treated with DRV/r-based regimens (12.4% vs. 22.5%, respectively). In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, mean reductions in fasting low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (HDL-C) at Week 24 were significantly greater in people who received DOR/3TC/TDF compared with the baseline PI-based regimen with 3TC/TDF ( $P < 0.0001$ ).<sup>12</sup> The reduction in fasting lipids was maintained through Week 144 in the extension arm of the DRIVE-SHIFT study.<sup>13</sup> Similarly, the 96 weeks of data from the DRIVE-FORWARD trial supported greater mean reductions in LDL-C (-14.6 mg/dL [95% CI, -18.2 to -11.0]) and non-HDL-C (18.4 mg/dL [95% CI, -22.5 to -14.3]) among participants in the DOR arm than among those in the DRV/r arm.<sup>10</sup> At Week 96 in the DRIVE-AHEAD trial, fasting HDL-C levels increased among participants in the EFV/FTC/TDF arm (mean increases of 10.8 and 15.0 mg/dL) but not among participants treated with DOR/3TC/TDF (-0.6 and -2.1 mg/dL), respectively, while the mean changes from baseline in total cholesterol/HDL-C ratio were similar between both arms<sup>11</sup> (-0.12 for DOR/3TC/TDF and -0.10 for EFV/FTC/TDF; treatment difference, -0.04; 95% CI, -0.23-0.15).

In the IMPAACT 2014 study of 43 treatment-experienced and 2 ARV-naive adolescents aged 12 to <18 years on DOR/3TC/TDF at Week 24, there were no Grade 3 or 4 AEs, serious AEs, or premature study drug discontinuation due to AEs.<sup>4</sup>



## Efavirenz (EFV, Sustiva)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Capsules: 50 mg, 200 mg</p> <p>Tablet: 600 mg</p> <p><b>Generic Formulations</b></p> <ul style="list-style-type: none"> <li>• 50-mg and 200-mg capsules</li> <li>• 600-mg tablet</li> </ul> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>• [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Symfi and generic] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg</li> </ul> <p>When using FDC tablets, refer to other sections of the <a href="#">Drug Appendix</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonatal Dose</b></p> <ul style="list-style-type: none"> <li>• Efavirenz (EFV) is not approved for use in neonates.</li> </ul> <p><b>Pediatric Dose</b></p> <ul style="list-style-type: none"> <li>• EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.</li> </ul> <p><i>Infants and Children Aged 3 Months to &lt;3 Years and Weighing ≥3.5 kg</i></p> <ul style="list-style-type: none"> <li>• The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) <b>does not recommend</b> the use of EFV in children aged 3 months to &lt;3 years due to highly variable pharmacokinetics in this age group.</li> </ul>	<ul style="list-style-type: none"> <li>• Rash, which is generally mild and transient</li> <li>• Central nervous system (CNS) symptoms, such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation, late-onset ataxia, and encephalopathy</li> <li>• Gynecomastia</li> <li>• Hepatotoxicity</li> <li>• Corrected QT prolongation</li> <li>• Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests.</li> </ul>
	<ul style="list-style-type: none"> <li>• EFV capsules and tablets can be swallowed whole, or EFV capsules can be administered by sprinkling the contents of an opened capsule on food, as described below.</li> </ul>

*Children Aged ≥3 Years and Weighing ≥10 kg*

**Once-Daily Doses of EFV by Weight**

Weight	EFV Dose <sup>a,b</sup>
10 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg
20 kg to <25 kg	300 mg
25 kg to <32.5 kg	350 mg
32.5 kg to <40 kg	400 mg
≥40 kg	600 mg

<sup>a</sup> The dose in mg can be dispensed in any combination of capsule strengths. Capsules may be administered by sprinkling the contents onto an age-appropriate food (see Special Instructions below).

<sup>b</sup> Some experts recommend a dose of EFV 367 mg per m<sup>2</sup> of body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see the Pediatric Use section below for details). Weight bands approximate a dose of EFV 367 mg per m<sup>2</sup> of body surface area, with a maximum dose of 600 mg.

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

- EFV 600 mg once daily

**[Atripla] EFV 600 mg/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)**

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

- One tablet once daily
- Take on an empty stomach.

**[Symfi] EFV 600 mg/Lamivudine (3TC)/TDF**

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

- One tablet once daily
- Take on an empty stomach.

**[Symfi Lo] EFV 400 mg/3TC/TDF**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose*

- One tablet once daily
- Take on an empty stomach.

- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- Administer EFV, Atripla, Symfi, or Symfi Lo on an empty stomach. Avoid administration with a high-fat meal because this has the potential to increase absorption.

**Instructions for Using the EFV Capsule as a Sprinkle Preparation with Food or Formula**

- Hold capsule horizontally over a small container and carefully twist open to avoid spillage.
- Gently mix capsule contents with 1 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing, and do not consume additional food or formula for 2 hours after administration.

**Metabolism/Elimination**

- Cytochrome P450 (CYP) 2B6 is the primary enzyme for EFV metabolism. CYP2A6, CYP3A4, CYP3A5, and uridine diphosphate glucuronosyltransferases also contribute to metabolism.
- CYP3A and CYP2B6 inducer *in vivo*
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP, particularly in CYP2B6. Slower metabolizers are at higher risk of toxicity. See the Therapeutic Drug Monitoring section below for information about the management of mild or moderate toxicity.

**EFV Dosing in Patients with Hepatic Impairment**

- EFV is **not recommended** for patients with moderate or severe hepatic impairment.

**Atripla, Symfi, and Symfi Lo Dosing in Patients with Renal Impairment**

- Because Atripla, Symfi, and Symfi Lo are FDC products containing TDF, lamivudine, and/or emtricitabine that require dose adjustments based on renal function, they should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.

<p><b>Note:</b> Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh <math>\geq 40</math> kg. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing <math>\geq 40</math> kg (see the Therapeutic Drug Monitoring section below).</p>	
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Coadministration of efavirenz (EFV) with drugs that are primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of EFV, resulting in lower plasma concentrations. There is potential for multiple drug interactions with EFV. Importantly, dose adjustment or the addition of ritonavir may be necessary when EFV is used in combination with atazanavir (ATV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).
- Before EFV is administered, a patient’s medication profile should be reviewed carefully for potential drug interactions with EFV.
- Corrected QT (QTc) prolongation has been observed with the use of EFV.<sup>1,2</sup> An alternative to EFV should be considered in patients who are receiving a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

## Major Toxicities

- *More common:* Skin rash and increased transaminase levels. Central nervous system (CNS) abnormalities—such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, and seizures—have been reported, primarily in adults. See [Table 17a. Antiretroviral Therapy—Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity](#) for information on managing these toxicities.
- *Rare:* QTc prolongation has been observed with the use of EFV, and Torsades de Pointes has been reported with EFV use.<sup>3</sup> An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance use) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.

## Resistance

The International Antiviral Society–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*

EFV has been approved by the U.S. Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged  $\geq 3$  months and weighing  $\geq 3.5$  kg. The FDA also has approved the use of Symfi Lo, the fixed-dose combination of EFV 400 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing  $\geq 35$  kg.

### *Efficacy in Clinical Trials*

EFV-based regimens have proven virologically superior or non-inferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, ATV, elvitegravir, raltegravir, and MVC.<sup>4-10</sup> EFV was shown to be inferior to dolutegravir (DTG) in the SINGLE trial in adults, which compared the virologic response of DTG plus abacavir/3TC with **that** of EFV/TDF/emtricitabine (FTC) at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the EFV group.<sup>11</sup>

In clinical trials in adults and children with HIV, EFV used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. FDA approval of Symfi (EFV 600 mg/3TC/TDF) was based on the results from a clinical trial that compared the use of TDF with the use of stavudine when each drug was administered with 3TC and EFV.<sup>12</sup> This trial showed that these regimens were similarly effective. The 96-week results of the Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy (ENCORE) 1 trial, a randomized trial in adults, showed that EFV 400 mg used in combination with TDF and FTC was non-inferior to EFV 600 mg used in combination with TDF and FTC.<sup>13</sup> EFV used in combination either with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety comparable to what has been seen in adults.<sup>14-16</sup>

FDA approval of Symfi Lo was based on a comparison between EFV 400 mg and EFV 600 mg, both taken with FTC 200 mg plus TDF 300 mg in 630 ARV-naive adult participants with a mean age of 36 years (range 18–69 years). Sixty-eight percent of participants were male, 37% were of African heritage, 33% were of Asian ethnicity, 17% were Hispanic, and 13% were White. This study showed similar rates of viral load suppression and toxicities among participants in each group.<sup>13</sup> Because EFV clearance is related to age and CYP2B6 polymorphisms, and because allele frequency varies by ethnicity, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) suggest using therapeutic drug monitoring (TDM) when using Symfi Lo in pediatric patients weighing  $\geq 40$  kg.

### *Pharmacokinetics: Pharmacogenomics*

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of EFV may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for EFV metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher EFV levels in these patients than in those with the G/G or G/T genotypes.<sup>17-21</sup> CYP2B6-516-T/T allele frequency varies by ethnicity. In a study of adults from the United States and Italy, this allele had a frequency of 24.4% among White participants, 31.3% among Black participants, and 34.9% among Hispanic participants.<sup>22</sup> A retrospective study of pediatric patients in a multiethnic, high-income setting

confirmed that EFV plasma concentrations can vary among patients. The interindividual variability could be explained in large part by polymorphisms in drug metabolizing genes, as well as by age at treatment initiation and time since treatment initiation.<sup>23</sup> International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1070 has shown that aggressive dosing with approximately 40 mg/kg of EFV using opened capsules resulted in therapeutic EFV concentrations in 58% of children aged <3 years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.<sup>21,24</sup> Optimal dosing may require pre-treatment CYP2B6 genotyping in children aged <3 years (see Pharmacokinetics and Dosing: Infants and Children Aged <3 Years below).<sup>20,21,24</sup>

Other variants—CYP2B6 alleles and variant CYP2A6 alleles—have been found to influence EFV concentrations in adults and children.<sup>20,25-28</sup>

### ***Pharmacokinetics and Dosing: Infants and Children Aged <3 Years***

The Panel **does not recommend** the use of EFV in children aged 3 months to <3 years. Pharmacokinetic (PK) data in children aged <3 years or weighing <14 kg have shown that it is difficult to achieve target trough concentrations ( $C_{trough}$ ) in this age group.<sup>18,29</sup> IMPAACT P1070 studied children aged <3 years with HIV and tuberculosis (TB) coinfection using doses of EFV that were determined by weight band based on CYP2B6-516-G/G and -G/T genotypes: children with G/G and G/T genotypes were considered extensive metabolizers (EMs), and children with T/T genotypes were considered slow metabolizers (SMs) (see [Table A](#) below). When doses were used without regard to genotype, a dose of approximately 40 mg/kg per day resulted in therapeutic EFV concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of participants with T/T genotypes. This dose is higher than the FDA-approved dose of EFV.<sup>24</sup> Therefore, doses were modified so that infants and young children with the T/T genotype received a reduced dose. The doses listed for P1070 in [Table A](#) are investigational.

A study evaluated the PK of EFV in children aged <3 years who had TB/HIV coinfection and were receiving anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. The findings from this study reinforced the use of CYP2B6-516 genotype-directed EFV dosing and showed that, in general, the EFV weight-band dose did not need to be modified further for children aged <40 months.<sup>21,30</sup>

## ***Investigational Dosing for Children Aged 3 Months to <3 Years by CYP2B6 Genotype***

**Table A. Comparison of Efavirenz Doses Used in P1070 and the FDA-Recommended Doses**

Weight	Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (EMs) <sup>a</sup>	Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (SMs) <sup>a</sup>	FDA-Approved Dosing for Children Aged 3 Months to <3 Years (without Regard to CYP2B6 Genotype)
5 kg to <7 kg	300 mg	50 mg	150 mg
7 kg to <7.5 kg	400 mg	100 mg	150 mg
7.5 kg to <10 kg	400 mg	100 mg	200 mg
10 kg to <14 kg	400 mg	100 mg	200 mg
14 kg to <15 kg	500 mg	150 mg	200 mg
15 kg to ≤17 kg	500 mg	150 mg	250 mg

<sup>a</sup> Investigational doses are based on the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) study P1070. Evaluation of the CYP2B6 genotype is required before initiating efavirenz (EFV). Therapeutic drug level monitoring is recommended, with a trough concentration measured 2 weeks after initiating EFV and again at age 3 years for a possible dose adjustment.

**Source:** Bwakura Dangarembizi M, Samson P, Capparelli EV, et al. Establishing dosing recommendations for efavirenz in HIV/TB-coinfected children younger than 3 years. *J Acquir Immune Defic Syndr.* 2019;81(4):473-480.

**Key:** CYP = cytochrome P450; EM = extensive metabolizer; SM = slow metabolizer

The FDA-approved doses of EFV for use in infants and children aged 3 months to <3 years were derived from a population PK model that was based on data from older participants in the Pediatric AIDS Clinical Trials Group (PACTG) 1021 and PACTG 382, as well as from data collected during AI266-922, a study that assessed the PK, safety, and efficacy of using capsule sprinkles in children aged 3 months to 6 years (see [Table A](#) above). The FDA-approved doses are lower than the CYP2B6 EM doses and higher than the CYP2B6 SM doses from the P1070 study. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic EFV target concentrations on FDA-indicated doses, according to the participants' genotypes.<sup>24</sup> The study reported that an estimated one-third of EM children who received the FDA-approved dose would experience subtherapeutic EFV exposures, and more than half of SM children who received the FDA-approved dose would have area under the curve (AUC) values that were above the target range.

In another study, PK data modeling was used to determine the impact of the CYP2B6 genotype in infants and children, as well as mothers and breastfeeding infants.<sup>31</sup> These data were derived from studies of African populations and included data from IMPAACT P1070. In these models, the FDA-approved doses of EFV were approximated by the models for dosing in children aged 3 months to <3 years who were EMs. The investigational doses from IMPAACT P1070 were approximated by the models for dosing in children aged 3 months to <3 years who were SMs.

The Panel **does not recommend** use of EFV in children aged 3 months to <3 years due to highly variable PK in this age group.



## ***Pharmacokinetics: Children Aged ≥3 Years and Adolescents***

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, EFV concentrations can be suboptimal.<sup>17,32-36</sup> Therefore, some experts recommend using TDM in patients who are receiving EFV and possibly using higher doses in young children, especially in certain clinical situations, such as virologic rebound or lack of response in an adherent patient. In one study in which the EFV dose was adjusted in response to measurement of the AUC, the median administered dose was EFV 13 mg/kg (367 mg per m<sup>2</sup> of body surface area), and the range was from 3 mg/kg to 23 mg/kg (69–559 mg per m<sup>2</sup> of body surface area).<sup>37</sup>

## ***Toxicity: Children Versus Adults***

The toxicity profile for EFV differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.<sup>38</sup> The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare.

Multiple studies in adults have shown that EFV use is associated with low vitamin D levels, and several studies have found an association between EFV use and low bone mineral density.<sup>39-42</sup> EFV induces CYP3A4 and CYP24 enzymes that may affect vitamin D homeostasis. Because of these findings, the Panel recommends measurement of vitamin D in patients receiving EFV and vitamin D supplementation for those with vitamin D deficiency (see [Table 17j. Antiretroviral Therapy—Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis](#)).

In adults, CNS symptoms are commonly reported and affected 29.6% of patients in one meta-analysis of randomized trials.<sup>43</sup> These symptoms usually occur early in treatment and rarely require drug discontinuation, but they sometimes can persist for months. Administering EFV at bedtime appears to decrease the occurrence and severity of these neuropsychiatric AEs. For patients who can swallow capsules or tablets, ensuring that EFV is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. In several studies, the incidence of neuropsychiatric AEs was correlated with EFV plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.<sup>44-47</sup> The ENCORE1 study in adults demonstrated that a dose of EFV 400 mg is associated with fewer AEs and a non-inferior virologic response when compared with the recommended 600-mg dose of EFV.<sup>13,48</sup> A Tanzanian study of children aged 6 to 12 years showed that those who were receiving EFV, especially doses of EFV that were higher than or equal to those recommended by the World Health Organization, had more anxiety and more difficulty concentrating at school than children who were receiving alternative ARV medications.<sup>49</sup> Adverse CNS events occurred in 14% of children who received EFV in clinical studies<sup>50</sup> and in 30% of children<sup>51</sup> with plasma EFV concentrations >4 mg/L. Late-onset neurotoxicity, including ataxia and encephalopathy, may occur months to years after initiating EFV. Some events of late-onset neurotoxicity have occurred in patients with certain CYP2B6 genetic polymorphisms who received standard doses of EFV. These polymorphisms have been associated with slow metabolism of EFV and increased EFV levels (see the [package insert for EFV](#)).

An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the Strategic Timing of AntiRetroviral Treatment (START) Trial, a prospective analysis of adults.<sup>52,53</sup> This association, however, was not found in the analyses



of two large observational cohorts,<sup>54,55</sup> and no cases of suicide were reported in a systematic review of randomized trials.<sup>43</sup> In patients with preexisting psychiatric conditions, EFV should be used cautiously.

### ***Toxicity: QTc Prolongation***

The effect of EFV on the QTc interval was evaluated in a study of 58 healthy adult participants; a variety of CYP2B6 polymorphisms was represented within this group. A positive relationship between EFV concentration and QTc prolongation was observed.<sup>1</sup> Clinicians should consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in patients who are at higher risk for Torsades de Pointes.<sup>2</sup>

### ***Therapeutic Drug Monitoring***

It is reasonable for a clinician to use TDM to determine whether a patient is experiencing toxicity, because the concentration of EFV is higher than the normal therapeutic range for some toxicities.<sup>56,57</sup> Dose reduction or drug discontinuation would be considered appropriate management of drug toxicity. Dose reduction is best performed in consultation with an expert in pediatric HIV. Also, TDM should be considered when administering EFV to children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. TDM should also be considered when using a lower dose of EFV—such as the dose found in Symfi Lo—in children weighing  $\geq 40$  kg. Two weeks after initiating EFV in patients aged <3 years, clinicians should measure the plasma concentration of EFV. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting the dose. If a child initiated EFV at an investigational dose at <3 years of age, some experts would also measure plasma concentration at age 3 years, after the child transitions to the recommended dose for children aged  $\geq 3$  years.

The currently accepted minimum effective concentration of EFV is a mid-dose concentration at 12 hours postdose ( $C_{12h}$ ) of  $>1$  mg/L in adults, and concentrations of  $>4.0$  mg/L are associated with CNS side effects.<sup>45</sup> However, the validity of using a single target has been called into question.<sup>58</sup> In addition, a lower limit of  $C_{12h} >0.7$  mg/L was most predictive of virologic outcome in a study of 180 adults.<sup>59</sup> Findings from a study of 128 African children (aged 1.7–13.5 years) suggest that the concentration at 24 hours ( $C_{24h}$ ) threshold for increased risk of unsuppressed viral load is  $C_{24h} 0.65$  mg/L.<sup>60</sup>

## Etravirine (ETR, Intelence)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations											
<p>Tablets: 25 mg, 100 mg, 200 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>											
Dosing Recommendations	Selected Adverse Events										
<p><b>Neonate and Infant Dose</b></p> <ul style="list-style-type: none"> <li>Etravirine (ETR) is not approved for use in neonates or infants.</li> </ul> <p><b>Child Dose</b></p> <ul style="list-style-type: none"> <li>ETR is not approved for use in children aged &lt;2 years.</li> </ul> <p><b>ETR Dosing Table for Antiretroviral Therapy–Experienced Children and Adolescents Aged 2 to 18 Years and Weighing ≥10 kg</b></p> <table border="1"> <thead> <tr> <th>Body Weight</th> <th>Twice-Daily Dose</th> </tr> </thead> <tbody> <tr> <td>10 kg to &lt;20 kg</td> <td>100 mg</td> </tr> <tr> <td>20 kg to &lt;25 kg</td> <td>125 mg</td> </tr> <tr> <td>25 kg to &lt;30 kg</td> <td>150 mg</td> </tr> <tr> <td>≥30 kg</td> <td>200 mg</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>ETR is approved for use in children and adolescents who are treatment experienced. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that ETR is used as part of a regimen that includes a ritonavir (RTV)-boosted protease inhibitor (PI) (see Efficacy in Clinical Trials and Drug Interactions below).</li> <li>Cobicistat-boosted PIs, non-nucleoside reverse transcriptase inhibitors, bictegravir, and elvitegravir/cobicistat should not be used with ETR. Raltegravir and dolutegravir should only be used with ETR with RTV-boosted atazanavir, darunavir, or lopinavir.</li> </ul> <p><b>Adult Dose for Antiretroviral Therapy–Experienced Patients</b></p> <ul style="list-style-type: none"> <li>ETR 200 mg twice daily with food.</li> </ul>	Body Weight	Twice-Daily Dose	10 kg to <20 kg	100 mg	20 kg to <25 kg	125 mg	25 kg to <30 kg	150 mg	≥30 kg	200 mg	<ul style="list-style-type: none"> <li>Nausea</li> <li>Diarrhea</li> <li>Rash, including Stevens-Johnson syndrome</li> <li>Hypersensitivity with rash; constitutional symptoms; and, sometimes, organ dysfunction, including hepatic failure</li> </ul>
Body Weight	Twice-Daily Dose										
10 kg to <20 kg	100 mg										
20 kg to <25 kg	125 mg										
25 kg to <30 kg	150 mg										
≥30 kg	200 mg										
	Special Instructions										
	<ul style="list-style-type: none"> <li>ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.</li> <li>Always administer ETR with food. Area under the curve of ETR is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to ETR.</li> <li>Swallowing ETR tablets whole is the preferred means of administration. Although the package insert contains instructions for dispersing ETR tablets in water or other liquids, using this administration method generally results in lower ETR exposures compared with swallowing tablets whole. Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as developmentally able.</li> </ul>										
	Metabolism/Elimination										
	<ul style="list-style-type: none"> <li>ETR is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.</li> <li>ETR is involved in multiple interactions with antiretroviral agents and other drugs (see Drug Interactions below).</li> </ul>										

	<p><b>ETR Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required when using ETR in patients with mild or moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.</li> </ul> <p><b>ETR Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required when using ETR in patients with renal impairment.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Etravirine (ETR) is associated with multiple drug interactions. A patient’s medication profile should be carefully reviewed for potential drug interactions before ETR is administered.
- ETR should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, unboosted protease inhibitors (PIs), or cobicistat-boosted PIs.<sup>1</sup>
- ETR should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine [NVP], efavirenz [EFV], rilpivirine, doravirine).
- ETR should not be administered** with bictegravir or elvitegravir/cobicistat. ETR reduces the trough concentration of raltegravir<sup>2</sup> (RAL) and dolutegravir (DTG). RAL and DTG should be used with ETR only when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.

## Major Toxicities

- More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly during the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with ETR. However, patients who have a history of severe rash with prior NNRTI use **should not receive ETR**.
- Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme all have been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional symptoms and organ dysfunction, including hepatic failure. Discontinue ETR immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinicians should monitor a patient’s clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use ETR after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using NVP or EFV **should not receive ETR**.

## Resistance

The International AIDS Society–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*

ETR is approved by the U.S. Food and Drug Administration (FDA) for use in antiretroviral therapy (ART)–experienced children and adolescents aged 2 to 18 years.

### *Efficacy in Clinical Trials*

In the Paediatric study of Intelence As an NNRTI Option (PIANO) study,<sup>3</sup> ART-experienced children aged 6 years to <18 years received ETR with a ritonavir (RTV)-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm<sup>3</sup> from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, whereas only 48% of adolescents aged 12 years to <18 years achieved a plasma viral load of <50 copies/mL.

In a retrospective study of 23 children and adolescents with multi-drug resistant HIV receiving ETR-based therapy in Spain, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.<sup>4</sup> A separate pooled analysis of treatment-experienced children and adolescents <18 years of age on ETR-based therapy showed 69% (85 of 124 patients) with follow-up data through 12 months achieved HIV RNA <50 copies/mL, and 80% (99 of 124 patients) achieved HIV RNA <400 copies/mL.<sup>5</sup>

In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1090 trial,<sup>6</sup> ART-experienced children aged ≥2 years to <6 years received ETR with an RTV-boosted PI as part of an optimized background regimen. Participants received ETR at a dose of 100 mg twice daily (10 kg to <20 kg) or 125 mg twice daily (20 kg to <25 kg). At Week 48, 75% had an HIV-1 RNA <400 copies/mL or a >2-log reduction in HIV-1 RNA from baseline. The mean increase in CD4 count and CD4 percentage over 48 weeks was 298.5 cells/mm<sup>3</sup> and 5.2%, respectively. Due to the PIANO and IMPAACT P1090 study findings, if ETR is utilized to treat an ART-experienced child or adolescent, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that ETR is part of a regimen that includes an RTV-boosted PI plus an optimized background regimen.

## Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 to 17 years, 17 children were given ETR 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve through 12 hours postdose (AUC<sub>0–12h</sub>) and minimum plasma concentration—were lower than the corresponding parameters observed in adults during previous studies.<sup>7</sup> However, a higher dose (ETR 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean AUC<sub>0–12h</sub>) remained lower

in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either White or Black participants. In the PIANO study, children and adolescents with ETR concentrations in the lowest quartile (<2,704 ng·h/mL or pre-dose concentration [ $C_{0h}$ ] <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads <50 copies/mL) after 48 weeks of treatment than those with ETR concentrations in the upper three quartiles.<sup>3</sup>

**Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily with an Optimized Background Regimen, Including a Ritonavir-Boosted Protease Inhibitor**

Population	Mean ETR AUC <sub>0-12h</sub> (ng·h/mL)	Mean ETR C <sub>0h</sub> (ng/mL)
Children Aged 6–11 Years (n = 41)	5,684	377
Adolescents Aged 12–17 Years (n = 60)	4,895	325
Adults (n = 575)	5,506	393

Key: AUC<sub>0-12h</sub> = area under the curve from time zero to 12 hours postdose; C<sub>0h</sub> = pre-dose concentration; ETR = etravirine

Source: Kakuda TN, Brochot A, Green B, et al. Pharmacokinetics and pharmacokinetic/pharmacodynamic relationships of etravirine in HIV-1-infected, treatment-experienced children and adolescents in PIANO. *J Clin Pharmacol.* 2016;56(11):1395-1405. Available at: <https://pubmed.ncbi.nlm.nih.gov/27060341>.

IMPAACT P1090 examined the PK and safety of ETR in treatment-experienced children with HIV aged  $\geq 2$  years to <6 years.<sup>6</sup> All participants received ETR as part of an optimized background regimen, which included an RTV-boosted PI. The tablets were swallowed whole or dispersed in liquid. ETR was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose, the geometric mean ETR AUC<sub>0-12h</sub> values fell below the target range of 60% of the values seen in adults. Subsequent participants were given twice-daily doses of ETR that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg twice daily, and children weighing 20 kg to <25 kg were given 125 mg twice daily.

The protocol-specified PK targets for ETR were achieved at these doses; the geometric mean AUC<sub>0-12h</sub> was 3,823 ng·hr/mL, which was within the target range of 2,713 ng·hr/mL to 6,783 ng·hr/mL (60% to 150% of the AUC<sub>0-12h</sub> value seen in adults). However, considerable intersubject variability was observed, with 5 (33.3%) of 15 participants having AUC<sub>0-12h</sub> values that were below the 10th percentile for the adult AUC<sub>0-12h</sub> range (<2,350 ng·hr/mL). The ETR AUC<sub>0-12h</sub> values were significantly lower in children who received dispersed tablets than in children who swallowed intact tablets: 2,919 ng·hr/mL (n = 11) versus 10,982 ng·hr/mL (n = 3), respectively ( $P = 0.0008$ ). The Panel recommends that children swallow tablets whole (rather than dispersed in liquid) as soon as developmentally able.

Six children with HIV who were aged 1 year to <2 years also were enrolled in IMPAACT P1090. Although the ETR exposures satisfied protocol-defined PK targets (AUC<sub>0-12h</sub> between 2,713 ng·hr/mL and 6,783 ng·hr/mL), they were lower in these children compared with historical data in adults and adolescents (geometric mean ETR AUC<sub>0-12h</sub> of 3,328 ng·hr/mL). Virologic failure, which was defined as a confirmed viral load of  $\geq 400$  copies/mL or less than a 2-log reduction in

HIV-1 RNA from baseline, occurred in four of six children by Week 48. Thus, the Panel does not recommend the use of ETR in those younger than 2 years of age.

Given that both the PIANO and IMPAACT P1090 trials were conducted in children receiving RTV-boosted PIs as part of their optimized background regimens, the Panel recommends using ETR as part of a regimen that includes an RTV-boosted PI.

## Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions that were deemed to be possibly related to the use of ETR. Rash (Grade 2 or higher) deemed possibly related to ETR occurred in 13% of pediatric participants and emerged at a median of 10 days, lasting a median of 7 days. The occurrence of any rash was observed more frequently in female patients (17 of 64 patients; 26.6%) than in male patients (6 of 37 patients; 16.2%).<sup>3</sup> In IMPAACT P1090, adverse drug reactions that were reported for children aged  $\geq 2$  years to  $< 6$  years were comparable in frequency, type, and severity to those reported for adults. Twelve participants (46.2%) developed Grade 1 or 2 rashes within the first 48 weeks of ETR, but no participant discontinued the study prematurely due to rash. Diarrhea occurred in 8 (30.8%) of 26 patients.<sup>6</sup>

## Nevirapine (NVP, Viramune)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Oral Suspension: 10 mg/mL</p> <p>Tablets: Immediate-release 200-mg tablets; extended-release (XR) 100-mg and 400-mg tablets</p> <p><b>Generic Formulations</b></p> <ul style="list-style-type: none"> <li>• 10-mg/mL suspension</li> <li>• Immediate-release 200-mg tablets</li> <li>• XR 400-mg tablets</li> </ul> <p>The oral suspension formulation of nevirapine (brand name Viramune) is not typically stocked in local pharmacies or hospitals. Clinicians should direct pharmacies to ask their drug wholesaler to order it from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Note:</b> Nevirapine (NVP) is often used as part of newborn antiretroviral regimens to prevent perinatal transmission of HIV. See <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection</a>.</p> <p><b>Child and Adolescent Dose</b></p> <ul style="list-style-type: none"> <li>• In most situations, NVP is given once daily for 2 weeks to allow autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged &lt;2 years.<sup>a</sup></li> <li>• See Special Considerations for Dosing: Neonates and Premature Infants below.</li> </ul> <p><b>Immediate-Release Tablets and Oral Suspension</b></p> <p><i>Gestational Age of 32 to &lt;34 Weeks</i></p> <ul style="list-style-type: none"> <li>• Birth to age 2 weeks: NVP 2 mg/kg per dose twice daily (no lead-in dosing)<sup>a</sup></li> <li>• Age 2 to 4 weeks: NVP 4 mg/kg per dose twice daily</li> <li>• Age 4 to 6 weeks: NVP 6 mg/kg per dose twice daily</li> <li>• Age &gt;6 weeks: NVP 200 mg/m<sup>2</sup> of body surface area (BSA) per dose twice daily; only make this dose increase for infants with confirmed HIV infection.</li> <li>• This dosing strategy is recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) based on the review of pharmacokinetic (PK) modeling and simulation</li> </ul>	<ul style="list-style-type: none"> <li>• Rash, including Stevens-Johnson syndrome</li> <li>• Symptomatic hepatitis, including fatal hepatic necrosis<sup>b</sup></li> <li>• Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock</li> </ul>
	<ul style="list-style-type: none"> <li>• The oral suspension must be shaken well before administering, and it should be stored at room temperature.</li> <li>• NVP can be given with or without food.</li> <li>• NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until the rash resolves (see Major Toxicities below).</li> <li>• Extended-release tablets <b>must</b> be swallowed whole. They cannot be crushed, chewed, or divided.</li> <li>• If NVP dosing is interrupted for &gt;14 days, NVP should be restarted with once-daily dosing for 14 days, followed by escalation to the full twice-daily regimen (see Dosing Considerations: Lead-In Dosing below).</li> </ul>



data. This dosing strategy has not been evaluated in clinical trials and is not approved by the U.S. Food and Drug Administration (FDA).

*Gestational Age of 34 to <37 Weeks*

- Birth to age 1 week: NVP 4 mg/kg per dose twice daily (no lead-in dosing)<sup>a</sup>
- Age 1 week to 4 weeks: NVP 6 mg/kg per dose twice daily
- Age >4 weeks: NVP 200 mg/m<sup>2</sup> of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

*Gestational Age of ≥37 Weeks to Age of <1 Month*

- Birth to age 4 weeks: NVP 6 mg/kg per dose twice daily (no lead-in dosing)<sup>a</sup>
- Age >4 weeks: NVP 200 mg/m<sup>2</sup> of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

*Aged ≥1 Month to <8 Years*

- NVP 200 mg/m<sup>2</sup> of BSA per dose twice daily after lead-in dosing.<sup>a</sup> In children aged ≤2 years, some experts initiate NVP without lead-in dosing (maximum dose of immediate-release tablets is NVP 200 mg twice daily).

*Aged ≥8 Years*

- NVP 120 mg to 150 mg/m<sup>2</sup> of BSA per dose twice daily after lead-in dosing<sup>a</sup> (maximum dose of immediate-release tablets is NVP 200 mg twice daily).
- When adjusting the dose for a growing child, the absolute dose need not be decreased as the child reaches age 8 years; rather, the absolute dose can be left static to achieve the appropriate mg-per-m<sup>2</sup> dose as the child grows, assuming no adverse effects emerge.

**Extended-Release Tablets**

*Aged ≥6 Years*

- Patients aged ≥6 years who are already taking immediate-release NVP tablets twice daily can be switched to extended-release NVP tablets without lead-in dosing.<sup>a</sup>

**Body Surface Area Dosing for Extended-Release NVP Tablets**

Body Surface Area	Once-Daily Dose
0.58 m <sup>2</sup> to 0.83 m <sup>2</sup>	NVP 200 mg (two 100-mg tablets)
0.84 m <sup>2</sup> to 1.16 m <sup>2</sup>	NVP 300 mg (three 100-mg tablets)
≥1.17 m <sup>2</sup>	NVP 400 mg (one 400-mg tablet)

- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities below).

**Metabolism/Elimination**

- NVP is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a NVP dose is eliminated in urine as uridine diphosphate glucuronosyltransferase (UGT)-derived glucuronidated metabolites.

**NVP Dosing in Patients with Hepatic Impairment**

- NVP should not be administered to patients with moderate or severe hepatic impairment.

**NVP Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis**

- An additional dose of NVP should be given following each dialysis session.

<p><i>Adolescent and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.<sup>a,b</sup></li> </ul> <p><b>NVP Used in Combination with Lopinavir/Ritonavir (LPV/r)</b></p> <ul style="list-style-type: none"> <li>• A higher dose of LPV/r may be needed in patients who also are receiving NVP (see the <a href="#">Lopinavir/Ritonavir</a> section).</li> </ul>	
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<sup>a</sup> NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP induces cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians generally should initiate therapy with the immediate-release tablet formulation once daily instead of twice daily for the first 14 days of therapy. If no rashes or other adverse effects emerge after 14 days of therapy, increase the dose of NVP to the age-appropriate full dose of the immediate-release tablet formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged  $\geq 1$  month to  $< 8$  years is NVP 200 mg/m<sup>2</sup> of BSA once daily for the first 14 days, followed by NVP 200 mg/m<sup>2</sup> of BSA twice daily thereafter. However, in children aged  $\leq 2$  years, some experts initiate NVP without lead-in dosing (see the Dosing Considerations: Lead-In Dosing and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving the full twice-daily dose of the immediate-release tablets, extended-release tablets can be used without the lead-in period. Patients must swallow extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of NVP at the same time.** The dose should not exceed NVP 400 mg daily.

<sup>b</sup> Severe life-threatening and, in rare cases, fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure—has occurred in patients who were taking NVP. These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Nevirapine (NVP) is metabolized by and induces hepatic CYP3A and CYP2B6; autoinduction of metabolism occurs in 2 to 4 weeks of NVP dosing, leading to a 1.5-fold to twofold increase in NVP clearance. Multiple drug interactions with NVP are possible. Some genetic polymorphisms of CYP2B6 are associated with increased NVP plasma concentrations. The prevalence of CYP2B6 polymorphisms varies among populations and may contribute to differences in NVP exposure. See the [Efavirenz section](#) for more information on how polymorphisms can alter metabolic enzyme activity.
- NVP should not be coadministered to patients who are receiving atazanavir (ATV) (with or without ritonavir) because NVP substantially decreases ATV exposure.
- NVP increases the metabolism of lopinavir (LPV). A dose adjustment of LPV is recommended when the two drugs are coadministered (see the [Lopinavir/Ritonavir](#) section).
- Before NVP is initiated, a patient’s medication profile should be carefully reviewed for potential drug interactions.

## Major Toxicities

The following toxicities are seen with chronic dosing, not during single-dose NVP prophylaxis.

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and elevated hepatic transaminases. In the two largest case series of NVP-induced Stevens-Johnson syndrome in children, the incidence rate was estimated between 1.4% and 7.1%.<sup>1,2</sup> NVP should be **discontinued and not restarted** in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated levels of hepatic transaminases. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing NVP resistance with extended lead-in dosing is unknown, and this concern must be weighed against the current antiviral response and a patient's overall ability to tolerate the regimen.
- *Less common (more severe):* These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). Risk factors for NVP-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 count >250 cells/mm<sup>3</sup> in adult females and >400 cells/mm<sup>3</sup> in adult males). Children with CD4 percentages >15% have a threefold increase in the risk of rash and hepatotoxicity after initiating NVP.<sup>3</sup> HSRs have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.
- *Less common (more severe):* In a cross-sectional study of 201 children with HIV aged 6 to 16 years, 43% of whom had hypertension, the use of NVP was associated with left ventricular hypertrophy (LVH) (adjusted odds ratio 3.14; confidence interval 1.13–8.72; *P* = 0.03) but not left ventricular diastolic dysfunction.<sup>4</sup> The median duration on antiretroviral therapy (ART) in this cohort was 4.7 years (interquartile range 2.6–6.4 years). Most participants (76.6%) were receiving a regimen that included two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, the use of NVP was not associated with LVH in a more recent study by the same authors. LVH has been associated with NVP use in adults.<sup>5,6</sup>

## Resistance

The International AIDS Society–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*

NVP is approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged  $\geq 15$  days) onward and remains a mainstay of ART, especially in resource-limited settings.<sup>7-15</sup> The extended-release tablet formulation has been approved by the FDA for use in children aged  $\geq 6$  years.

### *Efficacy in Clinical Trials*

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to NVP in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over NVP in children aged  $< 3$  years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics showed no differences in virologic outcomes between an NNRTI-based regimen (with either NVP or efavirenz [EFV]) and a protease inhibitor (PI)-based regimen in older children with HIV.<sup>16-22</sup>

In infants and children who were previously exposed to a single dose of NVP to prevent perinatal HIV transmission, NVP-based ART is less likely to control viral load than LPV/r-based ART. In IMPAACT P1060, 153 children with HIV and previous exposure to NVP for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine (ZDV) and lamivudine (3TC) plus either NVP or LPV/r. At 24 weeks post-randomization, 24% of children in the NVP arm had experienced virologic failure compared with 7% of children in the LPV/r arm ( $P = 0.0009$ ); virologic failure was defined as  $< 1 \log_{10}$  decrease in HIV RNA during Weeks 12 to 24 or HIV RNA  $> 400$  copies/mL at Week 24. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the NVP arm met a primary endpoint, compared with 22% of children in the LPV/r arm ( $P = 0.027$ ).<sup>19</sup> Similar results were reported in a randomized trial that compared NVP and LPV/r in children aged 6 to 36 months who had not been previously exposed to NVP. This finding suggests that LPV/r-based therapy is superior to NVP-based therapy for infants, regardless of past NVP exposure.<sup>16</sup>

Extended-release NVP tablets (400 mg) were approved by the FDA for use in children aged  $\geq 6$  years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release NVP tablets and had plasma HIV RNA  $< 50$  copies/mL prior to enrollment. Participants were stratified according to age (3 years to  $< 6$  years, 6 years to  $< 12$  years, and 12 years to  $< 18$  years). Participants received immediate-release NVP tablets for 11 weeks. Participants were then treated with NVP extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PK) were determined.<sup>23</sup> Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of extended-release NVP tablets through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with extended-release tablets,<sup>24</sup> all 39 participants continued to have plasma HIV RNA  $< 50$  copies/mL.

## General Dosing Considerations

Body surface area (BSA) has traditionally been used to guide NVP dosing in infants and young children. It is important to avoid underdosing NVP, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both NVP and EFV. Younger children (aged  $\leq 8$  years) have higher apparent oral clearance than older children. To achieve drug exposures that are comparable to those seen in children aged  $>8$  years, younger children require higher doses of NVP than older children.<sup>12,13</sup> Because of this, it is recommended that children aged  $<8$  years receive NVP 200 mg/m<sup>2</sup> of BSA per dose twice daily (the maximum dose of the immediate-release tablet formulation is NVP 200 mg twice daily) or NVP 400 mg/m<sup>2</sup> of BSA administered once daily as the extended-release tablet formulation (the maximum dose of the extended-release tablet formulation is NVP 400 mg once daily). For children aged  $\geq 8$  years, the recommended dose of the immediate-release tablet formulation is NVP 120 mg/m<sup>2</sup> of BSA per dose (with a maximum dose of NVP 200 mg) administered twice daily. The maximum dose of the extended-release tablet formulation is NVP 400 mg once daily for children aged  $\geq 6$  years.

When adjusting the dose for a growing child, the milligram dose need not be decreased (from NVP 200 mg to NVP 120 mg/m<sup>2</sup> of BSA) as the child reaches 8 years of age; rather, the milligram dose can be left static if no adverse effects emerge and the dose achieves the appropriate mg/m<sup>2</sup> of BSA dose as the child grows. Some practitioners dose NVP at 150 mg/m<sup>2</sup> of BSA every 12 hours or NVP 300 mg/m<sup>2</sup> of BSA once daily if using the extended-release tablets, regardless of age, as recommended in the FDA-approved product label. Regardless of age, the maximum dose should never exceed NVP 200 mg twice daily for immediate-release formulations of NVP or NVP 400 mg once daily for extended-release formulations of NVP.

### ***Dosing Considerations: Lead-in Dosing***

Underdosing during the lead-in period may have potentially contributed to the poorer performance of NVP in the IMPAACT P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to a re-evaluation of lead-in dosing in children who have never received NVP. Traditionally, NVP is initiated with an age-appropriate dose that is given only once daily instead of twice daily (NVP 200 mg/m<sup>2</sup> of BSA in infants aged  $\geq 15$  days and children aged  $<8$  years, using the immediate-release formulations) during the first 2 weeks of treatment to allow the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in NVP metabolism.

Studies have previously indicated potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.<sup>25</sup> The CHAPAS-1 trial<sup>26</sup> randomized 211 children to initiate ART with immediate-release NVP without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose once daily) for 2 weeks, followed by the standard twice-daily dosing of the immediate-release formulation of NVP. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and no difference emerged in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated NVP without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but most participants were able to continue NVP therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 count and virologic failure endpoints.

After children had been on NVP for 2 weeks, investigators conducted a substudy that examined NVP plasma concentrations 3 to 4 hours after a morning dose of NVP. Among children aged  $<2$  years, 3 of

23 children (13%) who initiated at full dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks compared with 7 of 22 children (32%) who initiated at half dose ( $P = 0.16$ ). No rash events occurred in the substudy group of participants aged <2 years; in the parent CHAPAS study, a strong age effect on rash occurrence was seen, with the risk of rash increasing with age. These findings suggest that a lead-in dose may not be necessary in young patients.<sup>27</sup>

The standard practice has been to reinitiate half-dose NVP for another 2 weeks in children who have interrupted therapy for 7 days or longer; however, given the current understanding of NVP resistance, the half-life of CYP enzymes,<sup>28</sup> and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends restarting full-dose NVP in children who interrupt therapy for 14 days or less.

### Special Considerations for Dosing: Neonates and Premature Infants

The PK and safety of NVP during the first weeks of life were evaluated as part of IMPAACT P1115. This study demonstrated that NVP dosed at 6 mg/kg twice daily for infants  $\geq 37$  weeks gestational age (GA) and 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily thereafter for infants 34 to <37 weeks GA achieved concentrations appropriate for treatment.<sup>29</sup> Among 438 infants (389 infants  $\geq 37$  weeks GA), measured NVP concentrations were above the minimum HIV treatment target (3 mcg/mL) in 90% of infants at Week 1 and 87% of infants at Week 2. Grade 3 and 4 adverse events possibly related to treatment occurred in 7% of infants (with neutropenia and anemia being the most common) but did not lead to NVP cessation.

PK modeling and simulation were performed with partial data from IMPAACT P1106 and P1115 to determine appropriate NVP dosing in premature infants 32 to <34 weeks GA. GA and postnatal age were significantly correlated with NVP oral clearance; thus, the authors recommended a GA-based starting dose for premature infants treated with NVP and a stepwise increase in dosing at 2-week intervals.<sup>30</sup> These data might underestimate potential drug toxicity in infants of 32 to <34 weeks GA because the doses used to develop the model were lower than the doses now recommended. NVP is shown to be safe in infants >34 weeks GA, so the risk of toxicity in infants 32 to <34 weeks GA seems low. The Panel considers that this risk–benefit ratio may justify the use of this dose in premature infants 32 to <34 weeks GA.

The Early Infant Treatment Study in Botswana started 40 infants with HIV  $\geq 35$  weeks GA on NVP 6 mg/kg twice daily (without lead-in dosing) along with ZDV and 3TC at a median age 2 days (range 1–5 days). NVP was switched to LPV/r at Week 2, 3, 4, or 5 according to delivery GA. Although NVP trough concentrations were below the therapeutic target (3,000 ng/mL) for 50% of 2-week measurements, 37 of 40 infants (92.5%) had an HIV RNA decline.<sup>31</sup> Among this cohort, 38 of 40 participants survived to 96 weeks with a preserved CD4 count and low reservoir, which was predicted by a low pre-ART reservoir size.<sup>32</sup> Providers who consider initiating treatment in premature infants or in infants aged <2 weeks should weigh the risks and benefits of using unapproved ART dosing and should incorporate case-specific factors, such as exposure to ARV prophylaxis.



## Rilpivirine (RPV, Edurant)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Tablet: 25 mg</p> <p><b>Fixed-Dose Combination Tablets</b></p> <ul style="list-style-type: none"> <li>• [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg</li> <li>• [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg</li> <li>• [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg</li> </ul> <p>When using fixed-dose combination (FDC) tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p><b>Co-packaged Formulations</b></p> <ul style="list-style-type: none"> <li>• [Cabenuva Kit] Cabotegravir 400 mg/2 mL (200 mg/mL) and rilpivirine 600 mg/2 mL (300 mg/mL) suspension for intramuscular injection</li> <li>• [Cabenuva Kit] Cabotegravir 600 mg/3 mL (200 mg/mL) and rilpivirine 900 mg/3 mL (300 mg/mL) suspension for intramuscular injection</li> </ul> <p>When using the co-packaged formulation, refer to the <a href="#">Cabotegravir</a> section for additional information.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonate and Infant Dose</b></p> <ul style="list-style-type: none"> <li>• Rilpivirine (RPV) is not approved for use in neonates or infants.</li> </ul> <p><b>Children Aged &lt;12 Years</b></p> <ul style="list-style-type: none"> <li>• RPV is not approved for use in children aged &lt;12 years (for more information, see the Pharmacokinetics section below).</li> </ul> <p><b>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>• RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naïve patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA &lt;50 copies/mL) with no history of virologic failure or resistance to RPV and other antiretroviral (ARV) drugs in the new regimen.</li> </ul>	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Insomnia</li> <li>• Headache</li> <li>• Rash, which can be severe and include DRESS (drug reaction [or rash] with eosinophilia and systemic symptoms)</li> <li>• Hepatotoxicity</li> <li>• Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance</li> </ul>



<p><b>[Complera] Emtricitabine (FTC)/Rilpivirine (RPV)/Tenofovir Disoproxil Fumarate (TDF)</b></p> <p><i>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with a meal in ART-naïve patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily also can be used to replace the current ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA &lt;50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.</li> </ul> <p><b>[Juluca] Dolutegravir (DTG)/RPV</b></p> <p><i>Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA &lt;50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.</li> <li>Not approved for use in children or adolescents (see the Simplification of Treatment section below).</li> </ul> <p><b>[Odefsey] FTC/RPV/Tenofovir Alafenamide (TAF)</b></p> <p><i>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with a meal in ART-naïve patients with HIV RNA ≤100,000 copies/mL. One tablet once daily also can be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA &lt;50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.</li> </ul> <p><b>[Cabenuva] Cabotegravir (CAB) and RPV Kit</b></p> <p><i>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>Cabenuva is a two-drug co-packaged product for intramuscular (IM) injection that is approved by the U.S. Food and Drug Administration as a complete regimen for the treatment of HIV-1 in patients with HIV RNA levels &lt;50 copies/mL on a stable ARV regimen with no history of treatment failure and no known or suspected resistance to CAB or RPV.</li> </ul>	<p style="text-align: center;"><b>Special Instructions</b></p> <ul style="list-style-type: none"> <li><b>Do not start</b> RPV in patients with HIV RNA &gt;100,000 copies/mL because of the increased risk of virologic failure.</li> <li>RPV concentrations are significantly increased when either RPV or DTG/RPV is administered with a moderate- or high-fat meal.<sup>1</sup> Patients must be able to take RPV (or DTG/RPV) with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).</li> <li><b>Do not use</b> RPV with other non-nucleoside reverse transcriptase inhibitors.</li> <li><b>Do not use</b> RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).</li> <li>Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.</li> <li>H2 receptor antagonists (e.g., cimetidine, famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.</li> <li>Use RPV with caution when coadministering it with a drug that has a known risk of prolonging the QTc interval or causing Torsades de Pointes (for more information, see <a href="#">CredibleMeds</a>).</li> <li>Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain TDF or TAF. Severe acute exacerbation of HBV infection can occur when TDF or TAF are discontinued (see the <a href="#">Tenofovir Disoproxil Fumarate</a> and <a href="#">Tenofovir Alafenamide</a> sections). Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with TDF or TAF is discontinued in patients with HBV.</li> <li>Refer to the <a href="#">Cabotegravir</a> section for special instructions when using CAB and RPV for IM injection.</li> </ul> <p style="text-align: center;"><b>Metabolism/Elimination</b></p> <ul style="list-style-type: none"> <li>Cytochrome P450 3A substrate</li> <li>Refer to the <a href="#">Cabotegravir</a> section for information about the IM CAB and RPV regimen.</li> </ul> <p><b>RPV Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is necessary in patients with mild or moderate hepatic impairment.</li> </ul>
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<ul style="list-style-type: none"> <li>• Oral lead-in dosing for at least 28 days can be used to assess tolerability prior to initiating IM CAB and RPV injections or patients can proceed directly to IM CAB and RPV on the last day of their current ARV regimen.</li> <li>• Refer to the <a href="#">Cabotegravir</a> section for dosing information.</li> <li>• Long-acting CAB and RPV for IM injection are not approved for children aged &lt;12 years.</li> </ul>	<p><b>RPV Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.</li> <li>• No dose adjustment is necessary in patients with mild or moderate renal impairment. However, RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events; renal dysfunction may alter drug absorption, distribution, and metabolism, leading to increased RPV concentrations.</li> <li>• The FDC tablet Complera <b>should not be used</b> in patients with creatinine clearance (CrCl) &lt;50 mL/min, and the FDC tablet Odefsey <b>should not be used</b> in patients with CrCl &lt;30 mL/min. Patients with CrCl &lt;30 mL/min who are taking Juluca should be monitored closely.</li> <li>• When using Complera, see the <a href="#">Tenofovir Disoproxil Fumarate</a> section of the guidelines; when using Odefsey, see the <a href="#">Tenofovir Alafenamide</a> section.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate, and concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before RPV is administered.
- Coadministering RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
  - Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
  - H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.
  - **Do not use** RPV with proton pump inhibitors.
- All the rifamycins significantly reduce RPV plasma concentrations; coadministration of rifampin and oral RPV is **contraindicated**. For patients who are concomitantly receiving rifabutin and oral RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal. Intramuscular (IM) RPV given with IM CAB is **contraindicated** with rifampin, rifabutin, and rifapentine.
- In a cohort of adolescent patients, RPV exposure was two to three times greater when RPV was administered in combination with darunavir/ritonavir (DRV/r) than when RPV was administered alone.<sup>2</sup>

## Major Toxicities

- *More common:* Insomnia, headache, rash
- *Less common (more severe):* Depression or mood changes, suicidal ideation

In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram (mcg) adrenocorticotrophic hormone (ACTH) stimulation test (peak cortisol level <18.1 mcg/dL). In a study of adolescents, 6 out of 30 patients (20%) developed this abnormality.<sup>3</sup> The clinical significance of these results is unknown.

- *Rare:* RPV drug-induced liver injury has been reported.<sup>4</sup>

## 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.

Transmitted drug resistance to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be present in infants and children who have recently received a diagnosis of HIV.

## Pediatric Use

### *Approval*

With the viral load and antiretroviral (ARV) resistance restrictions noted above, RPV (Edurant) used in combination with other ARV agents, the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera), the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF; Odefsey), and the long-acting regimen of cabotegravir (CAB) and RPV for IM injection (IM CAB and RPV; Cabenuva) are all approved by the U.S. Food and Drug Administration (FDA) for use in people aged  $\geq 12$  years and weighing  $\geq 35$  kg. The FDC tablet dolutegravir/rilpivirine (DTG/RPV; Juluca) **is not approved** for use in pediatric or adolescent patients at the time of this review.

### *Efficacy in Clinical Trials*

An RPV-containing regimen has been compared to an efavirenz (EFV)-containing regimen in two large clinical trials in adults—ECHO and THRIVE. In both studies, RPV was shown to be non-inferior to EFV. Patients with pretreatment HIV viral loads  $\geq 100,000$  copies/mL who received RPV had higher rates of virologic failure than those who received EFV. These findings resulted in FDA approval for initial therapy with RPV only in patients with HIV viral loads  $\leq 100,000$  copies/mL.<sup>5-8</sup>

A study of antiretroviral therapy (ART)-naïve adolescents aged 12 to 17 years demonstrated that RPV 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. In adolescents with baseline viral loads  $\leq 100,000$  copies/mL, 86% had a virologic response at 24 weeks and 79% had a virologic response at 48 weeks. In adolescents with baseline viral loads  $>100,000$  copies/mL, 38% had a virologic response at 24 weeks and 50% had a virologic response at 48 weeks.<sup>9</sup>

Patients must be able to take RPV on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation Odefsey is a small pill and can be useful for certain patients who have difficulty swallowing pills or want to switch from a multi-pill regimen and who do not have any drug-resistance mutations associated with components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years) who acquired HIV perinatally to receive FTC/RPV/TDF (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, 4 were on an NNRTI-based regimen, and 1 had not received ART. After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, maintained and achieved an undetectable viral load. None of the patients discontinued RPV-based therapy because of adverse events (AEs); no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved, and two adolescents with a history of insomnia and abnormal dreams while receiving EFV-based therapy did not report similar problems while receiving RPV-based therapy.<sup>10</sup>

Another study evaluated 102 virologically suppressed Thai adolescents who were switched from an EFV-based therapy to an RPV-based therapy. Ninety-four of the adolescents remained virologically suppressed through 48 weeks; six experienced virologic failure. Overall, RPV was well tolerated. No improvement in EFV-related symptoms (e.g., sleep, mood, dizziness, headache, concentration) was observed, and no change in quality of life or depression scores could be documented; however, there were significant improvements in some assessments of cognitive and executive function as measured at Week 24.<sup>11</sup>

### ***Pharmacokinetics***

The pharmacokinetics (PK), safety, and efficacy of RPV in children aged <12 years have not been established but are currently being studied in patients aged 6 years to <12 years and weighing  $\geq 17$  kg ([ClinicalTrials.gov identifier NCT00799864](https://clinicaltrials.gov/ct2/show/study/NCT00799864)). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has agreed that the use of RPV may be appropriate in certain children aged <12 years and weighing  $\geq 35$  kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to prescribing RPV for a child in this age and weight group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, Pediatric Study in Adolescents Investigating a New NNRTI TMC278 (PAINT), investigated a 25-mg dose of RPV given in combination with two NRTIs in ARV-naive adolescents aged 12 years to <18 years who weighed  $\geq 32$  kg and who had viral loads  $\leq 100,000$  copies/mL.<sup>9</sup> In the dose-finding phase of the study, 11 adolescents aged >12 years to  $\leq 15$  years and 12 adolescents aged >15 years to  $\leq 18$  years underwent intensive PK assessment after they took an observed dose of RPV with a meal. PK were comparable to those in adults; results are listed in the table below.<sup>12</sup>

**Table A. Rilpivirine Pharmacokinetics in Adults and Adolescents Aged 12 Years to <18 Years**

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily
Number of Participants Studied	679	34
<b>AUC<sub>24h</sub> (ng·h/mL)</b>		
Mean ± SD	2,235 ± 851	2,424 ± 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
<b>C<sub>0h</sub> (ng/mL)</b>		
Mean ± SD	79 ± 35	85 ± 40
Median (Range)	73 (2–288)	79 (7–202)

Source: Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2021. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/202022s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202022s014lbl.pdf).

Key: AUC<sub>24h</sub> = area under the curve after 24 hours; C<sub>0h</sub> = plasma concentration just prior to next dose; RPV = rilpivirine; SD = standard deviation

In a PK study of adolescents and young adults aged 13 to 23 years who received RPV,<sup>2</sup> RPV exposure was comparable to the exposure observed during the PAINT study in patients who received 25-mg doses of RPV without DRV/r and substantially higher than the exposure observed in those who received 25-mg doses of RPV with DRV/r (RPV area under the curve in this study was 6,740 ng·h/mL). No dose adjustments are currently recommended for adults when RPV is coadministered with DRV/r, where a similar twofold to threefold increase in RPV exposure has been reported.<sup>3</sup>

RPV has been reported to have fewer CNS AEs than EFV, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving EFV. However, concern exists that the prolonged half-life of EFV might result in residual drug levels that could have an impact on RPV levels. A study evaluated 20 Thai adolescents 4 weeks after they switched from EFV to RPV. The PK parameters of RPV in this study population were comparable to those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks, and no patients discontinued RPV because of AEs.<sup>13</sup>

### ***Simplification of Treatment***

Juluca is an FDC tablet that contains DTG 50 mg and RPV 25 mg. The results from two trials in adults (SWORD-1 and SWORD-2) supported FDA approval of DTG/RPV as a complete regimen for treatment simplification or maintenance therapy in certain patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations that are associated with DTG or RPV. The participants were randomized to receive DTG/RPV (“early switch”) or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.<sup>14</sup> After 52 weeks, the participants who had been

randomized to continue their suppressive ARV regimen were switched to DTG/RPV (“late switch”). At 148 weeks of treatment, 84% of the early switch patients and 90% of the late switch patients remained virologically suppressed, and only 11 patients receiving dual therapy (DTG/RPV) met virologic failure criteria. No integrase inhibitor resistance was identified.<sup>15</sup> More AEs were reported and more AEs led to treatment discontinuation in the DTG/RPV arm during the comparative randomized phase. In a subgroup of SWORD study patients whose original ARV regimen contained TDF, small but statistically significant increases in hip and spine bone mineral density were observed.<sup>16</sup> Although DTG/RPV as Juluca is not approved for use in adolescents, the doses of both component drugs that make up Juluca are approved for use in adolescents. This product may be appropriate for certain adolescents; however, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulties adhering to therapy, the Panel **does not recommend** using Juluca in adolescents and children until more data are available.

### ***Long-Acting Injectable Rilpivirine***

A long-acting IM injectable formulation of RPV has recently been approved for coadministration with IM CAB as a complete ARV regimen for children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg and adults with HIV RNA levels  $< 50$  copies/mL, on a stable ARV regimen, with no history of treatment failure, and no known or suspected resistance to CAB or RPV.<sup>17</sup> This formulation has been evaluated in adults as monthly or every-other-month IM injections following an initial oral lead-in daily dose for 4 weeks to assess toxicity.<sup>18-20</sup> These studies in adult patients demonstrated non-inferior efficacy to standard oral therapy and good participant satisfaction and tolerability through 96 weeks. A follow-on study demonstrated that dosing IM CAB and RPV every 2 months in virally suppressed participants provided similar safety and efficacy to monthly injections through 48 weeks.<sup>21</sup> Additionally, an extension of one study evaluated the benefit of oral lead-in therapy prior to initiating IM CAB and RPV, demonstrating that initial oral therapy can be optional based on the needs and desires of people initiating treatment.<sup>22</sup> [IMPAACT study 2017](#), More Options for Children and Adolescents (MOCHA), is currently evaluating the safety, tolerability, acceptability, and PK profile of IM CAB and RPV in adolescents weighing  $\geq 35$  kg and has reported acceptable PKs and safety for the single IM products administered monthly and good acceptability by both adolescents and their parents.<sup>23,24</sup> However, MOCHA has not completed evaluation of the dual injectable regimen long-term, and clinical experience with IM CAB and RPV remains limited. See the [Cabotegravir](#) section for more information about this regimen.

### ***Toxicity***

In the PAINT study, the observed AEs were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, headache). The incidence of depressive disorders was 19.4% (7 of 36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grade 3 and 4 depressive disorders was 5.6% (2 of 36 participants).<sup>3</sup>

Six out of 30 adolescents (20%) with a normal ACTH stimulation test at baseline developed an abnormal test during the trial. No serious AEs, deaths, or treatment discontinuations were attributed to adrenal insufficiency. The clinical significance of abnormal ACTH stimulation tests is not known, but this finding warrants further evaluation.<sup>3</sup>

### ***Crushing Tablets for Enteral Administration***

Some cases report DTG/RPV tablets' being crushed and successfully administered via an enteral tube.<sup>25</sup> If DTG/RPV is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.



# Appendix A: Pediatric Antiretroviral Drug Information

## Protease Inhibitors

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)

# Atazanavir (ATV, Reyataz)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations					
<p>Powder Packet: 50 mg/packet</p> <p>Capsules: 150 mg, 200 mg, 300 mg</p> <p><b>Generic Formulations</b></p> <ul style="list-style-type: none"> <li>150-mg, 200-mg, and 300-mg capsules</li> </ul> <p><b>Fixed-Dose Combination Tablets</b></p> <ul style="list-style-type: none"> <li>[Evotaz] Atazanavir 300 mg/cobicistat 150 mg</li> </ul> <p>Capsules and powder packets are not interchangeable.</p> <p>For additional information, see <a href="#">Drugs@FDA: FDA-Approved Drugs</a> or <a href="#">DailyMed</a>.</p>					
Dosing Recommendations	Selected Adverse Events				
<p><b>Neonate Dose</b></p> <ul style="list-style-type: none"> <li>Atazanavir (ATV) is not approved for use in neonates and infants aged &lt;3 months. ATV <b>should not be administered</b> to neonates because of risks associated with hyperbilirubinemia (e.g., bilirubin-induced neurologic dysfunction).</li> </ul> <p><b>Infant and Child Dose</b></p> <p><i>Powder Formulation of ATV<sup>a</sup></i></p> <ul style="list-style-type: none"> <li>The powder formulation of ATV must be administered with ritonavir (RTV).</li> <li>The powder formulation is not approved for use in infants aged &lt;3 months or weighing &lt;5 kg.</li> </ul> <p><b>ATV Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥15 kg<sup>a</sup></b></p> <table border="1"> <thead> <tr> <th>Weight</th> <th>Once-Daily Dose</th> </tr> </thead> <tbody> <tr> <td>15 kg to &lt;25 kg<sup>b</sup></td> <td>ATV 250 mg (five packets) plus RTV 100 mg (powder or tablet) with food</td> </tr> </tbody> </table> <p><i>Capsule Formulation of ATV<sup>a</sup></i></p> <ul style="list-style-type: none"> <li>ATV capsules are not approved for use in children aged &lt;6 years or weighing &lt;15 kg.</li> </ul>	Weight	Once-Daily Dose	15 kg to <25 kg <sup>b</sup>	ATV 250 mg (five packets) plus RTV 100 mg (powder or tablet) with food	<ul style="list-style-type: none"> <li>Indirect hyperbilirubinemia</li> <li>Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients</li> <li>Nephrolithiasis</li> <li>Increased serum transaminases</li> <li>Hyperlipidemia (occurs primarily with RTV boosting)</li> </ul>
Weight	Once-Daily Dose				
15 kg to <25 kg <sup>b</sup>	ATV 250 mg (five packets) plus RTV 100 mg (powder or tablet) with food				
	Special Instructions				
	<ul style="list-style-type: none"> <li>Administer ATV with food to enhance absorption.</li> <li>Capsules and powder packets <b>are not interchangeable</b>.</li> <li>Do not open capsules.</li> <li>Because ATV can prolong the PR interval of the electrocardiogram, use ATV with caution in patients with preexisting cardiac conduction system disease or with other drugs that are known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).</li> <li>ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that <b>increase</b> gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the <a href="#">ATV package insert</a>).</li> </ul>				

**Atazanavir/Ritonavir (ATV/r) Capsule Dosing Table for Children and Adolescents Aged ≥6 Years and Weighing ≥15 kg**

Weight	Once-Daily Dose
<15 kg	Capsules not recommended
15 kg to <35 kg	ATV/r 200 mg/100 mg, both with food <sup>c</sup>
≥35 kg	ATV/r 300 mg/100 mg, both with food <sup>c</sup>

**ART-Naive Patients Who Are Unable to Tolerate RTV**

*Child and Adolescent (Aged ≥13 Years and Weighing ≥40 kg) and Adult Dose*

- ATV 400 mg (capsule formulation only) once daily with food
- ATV powder is not an option because it must be administered with RTV.
- For the capsule formulation, the U.S. Food and Drug Administration (FDA) and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **do not recommend** the use of unboosted ATV in children aged <13 years.
- **Although the FDA does allow for unboosted ATV in adolescents aged ≥13 years and weighing ≥40 kg if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), the Panel does not recommend the use of unboosted ATV in this population. Unboosted ATV is not recommended because adolescents may require doses of ATV that are higher than those recommended for use in adults to achieve target drug concentrations** (see Pediatric Use below).

**ART-Naive and ART-Experienced Patients**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose*

- ATV/r 300 mg/100 mg once daily with food<sup>d</sup>
- Atazanavir/cobicistat (ATV/c) 300 mg/150 mg once daily with food, administered as single agents simultaneously or as the coformulated drug Evotaz<sup>e</sup>
- Both ATV/r and ATV/c must be used in combination with other antiretroviral drugs.

**[Evotaz] ATV/c**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose*

- One tablet once daily with food

- The plasma concentration and, therefore, the therapeutic effect of ATV can be expected to decrease substantially when ATV is coadministered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naïve patients who are receiving any PPI should receive a dose of that PPI that is equivalent to no more than a 20-mg dose of omeprazole. PPIs should be taken approximately 12 hours before taking boosted ATV. Coadministration of ATV with PPIs is **not recommended** in ART-experienced patients.

- Patients with hepatitis B or C virus infections and patients who **have** marked elevations in transaminase levels before treatment may have an increased risk of further elevations in transaminase levels or hepatic decompensation.

**Powder Administration**

- ATV oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.
- Mix ATV oral powder with at least 1 tablespoon of soft food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup. For young infants (aged <6 months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and administered using an oral dosing syringe.
- Administer RTV immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

**Metabolism/Elimination**

- ATV is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate **glucuronosyl transferase** 1A1.

**ATV Dosing in Patients with Hepatic Impairment**

- ATV should be used with caution in patients with mild or moderate hepatic impairment. Consult the manufacturer's prescribing information for the dose adjustment in patients with moderate impairment.
- **ATV should not be used** in patients with severe hepatic impairment.

**ATV Dosing in Patients with Renal Impairment**

- No dose adjustment is required for patients with renal impairment.

- |  |   |
|--|---|
|  | <ul style="list-style-type: none"> <li>• ATV should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.</li> </ul> |
|--|---|

<sup>a</sup> mg/kg dosing is higher for the ATV powder packets than for the capsules. In P1020A, children of similar age and size who were taking ATV powder had lower exposures than those who were taking ATV capsules.

<sup>b</sup> Children weighing  $\geq 25$  kg who cannot swallow ATV capsules may receive ATV 300-mg oral powder (six packets) plus RTV 100-mg oral solution, both administered once daily with food.

<sup>c</sup> Either RTV capsules or RTV oral solution can be used.

<sup>d</sup> Adult patients who cannot swallow capsules may take ATV oral powder once daily with food using the adult dose for the capsules. ATV oral powder should be administered with RTV.

<sup>e</sup> See the [Cobicistat](#) section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat (COBI) and the combination of COBI and TDF.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Atazanavir (ATV) is both a substrate and an inhibitor of the cytochrome P450 (CYP) 3A4 enzyme system and has significant interactions with drugs that are highly dependent on CYP3A4 for metabolism. ATV also competitively inhibits CYP1A2 and CYP2C9. ATV is a weak inhibitor of CYP2C8. ATV inhibits the glucuronidation enzyme uridine diphosphate glucuronosyl transferase (UGT1A1). Because of the potential for multiple drug interactions with ATV, a patient's medication profile should be carefully reviewed for potential drug interactions before administering ATV.
- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir disoproxil fumarate (TDF) decreases ATV plasma concentrations, and the effect of tenofovir alafenamide (TAF) on unboosted ATV is unknown. Thus, only atazanavir/ritonavir (ATV/r) or atazanavir/cobicistat (ATV/c) should be used in combination with TDF or TAF.
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz (EFV), etravirine (ETR), and nevirapine (NVP) decrease ATV plasma concentrations significantly. NVP and ETR **should not be administered** to patients who are receiving ATV (with or without a booster). Although the combination of EFV and ATV/r is not commonly used in clinical practice, EFV may be used in combination with ritonavir (RTV)-boosted ATV 400 mg in antiretroviral therapy (ART)-naive patients. ATV/r should be taken with food, and EFV should be taken on an empty stomach, preferably at bedtime. Coadministering ATV/r and EFV in ART-experienced patients **is not recommended** because this combination is expected to result in suboptimal ATV exposure in these patients.
- *Integrase strand transfer inhibitors:* ATV is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir (RAL). This interaction may not be clinically significant.
- *Absorption:* ATV absorption is dependent on low gastric pH. The dose for ATV should be adjusted when it is administered with medications that **increase** gastric pH. Guidelines for the appropriate doses of ATV to use with antacids, H<sub>2</sub> receptor antagonists, and proton-pump inhibitors in adults are complex and can be found in the [package insert for ATV](#). No information is available on the appropriate doses of ATV to use in children when the drug is coadministered with medications that **increase** gastric pH.

- Coadministering cobicistat (COBI)—a CYP3A4 inhibitor—and medications that are metabolized by CYP3A4 may increase the plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) that are associated with the concomitant medications. Coadministration of COBI, ATV, and CYP3A4 inducers may lead to lower exposures of COBI and ATV, a loss of efficacy of ATV, and possible development of resistance.<sup>1</sup> Coadministering COBI and ATV with some antiretroviral (ARV) agents (e.g., with ETR, with EFV in ART-experienced patients, or with another ARV drug that requires pharmacokinetic [PK] enhancement, such as another protease inhibitor [PI] or elvitegravir) may result in decreased plasma concentrations of that agent, leading to loss of therapeutic effect and the development of resistance.

## Major Toxicities

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesia.
- *Less common:* Prolongation of the electrocardiogram PR interval. Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but second-degree AV block has been reported. Rash is generally mild or moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. The use of ATV/r is associated with lipid abnormalities, but to a lesser extent than with other boosted PIs.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Chronic kidney disease, including biopsy-proven cases of granulomatous interstitial nephritis that were associated with the deposition of ATV drug crystals in the renal parenchyma have occurred. Nephrolithiasis and cholelithiasis have been reported. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased risk of hepatotoxicity).

## Resistance

The International Antiviral Society–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*

ATV is approved by the U.S. Food and Drug Administration (FDA) for use in infants (aged  $\geq 3$  months and weighing  $\geq 5$  kg), children, and adolescents. Because RTV oral solution is no longer commercially available, use of ATV/r is limited to children weighing  $\geq 15$  kg who can use the RTV 100 mg powder packet or 100 mg tablet. ATV coformulated with COBI (as Evotaz) has been approved by the FDA for use in pediatric patients weighing  $\geq 35$  kg.

## ***Efficacy***

Studies in ART-naive adults have shown that ATV/r is as effective as EFV and lopinavir/ritonavir (LPV/r) when these drugs are administered with two NRTIs.<sup>2-5</sup> In AIDS Clinical Trials Group (ACTG) A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or RAL, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, the regimen that contained ATV/r was discontinued more frequently than the other regimens because of toxicity but most often because of hyperbilirubinemia or gastrointestinal complaints.<sup>6</sup>

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)/Pediatric AIDS Clinical Trials Group (PACTG) P1020 enrolled 195 ART-naive and ART-experienced patients with HIV aged 3 months to 21 years. Capsule and powder formulations of ATV given with and without RTV boosting were investigated in this open-label study; area under the curve (AUC) targeting was used to direct dose finding. Of the 195 patients enrolled, 142 patients received ATV-based treatment at the final recommended dose. Among these patients, 58% were ART-naive. At Week 48, 69.5% of the ART-naive patients and 43.3% of the ART-experienced patients had HIV viral loads  $\leq 400$  copies/mL.<sup>7,8</sup> (Kiser, Fletcher et al. 2008, Kiser, Rutstein et al. 2011)

Two open-label clinical trials in infants and children, PRINCE-1 and PRINCE-2, studied a powder formulation of ATV that was administered once daily and boosted with liquid RTV.<sup>9-11</sup> In total, 134 infants and children aged  $\geq 3$  months and weighing between 5 and 35 kg were evaluated. Using a modified intent-to-treat analysis, 28 of 52 ARV-naive patients (54%) and 41 of 82 ART-experienced patients (50%) had HIV RNA  $< 50$  copies/mL at Week 48. The median increase from baseline in absolute CD4 T lymphocyte cell count at 48 weeks of therapy was 215 cells/mm<sup>3</sup> (a 6% increase) in ARV-naive patients and 133 cells/mm<sup>3</sup> (a 4% increase) in ARV-experienced patients.

## ***Pharmacokinetics and Dosing***

### **Oral Capsule**

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of RTV boosting, ATV can achieve protocol-defined PK targets—but only when used at higher doses (on a mg per kg body weight or mg per m<sup>2</sup> of body surface area basis) than the doses that are currently recommended in adults. In IMPAACT/PACTG 1020A, children aged  $> 6$  years to  $< 13$  years required a dose of 520 mg per m<sup>2</sup> of body surface area per day of the ATV capsule formulation to achieve PK targets.<sup>8</sup> Unboosted ATV at this dose was well tolerated in those aged  $< 13$  years who were able to swallow capsules.<sup>12</sup> The approved dose for adults is ATV 400 mg once daily without RTV boosting; however, adolescents aged  $> 13$  years required a dose of ATV 620 mg per m<sup>2</sup> of body surface area per day.<sup>8</sup> In this study, the AUCs for the unboosted arms were similar to those seen in the ATV/r arms, but the maximum plasma concentration ( $C_{max}$ ) was higher and the minimum plasma concentration ( $C_{min}$ ) was lower in the unboosted arms. Median doses of ATV, both with and without RTV boosting, from IMPAACT/PACTG 1020A are outlined in [Table A](#) below. When administering unboosted ATV to pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate ATV plasma concentrations have been achieved. A minimum target trough concentration for ATV is 150 ng/mL.<sup>13</sup> Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted ATV PK in ART-experienced children, concluded that once-daily ATV 400 mg provided suboptimal exposure and that

administering higher, unboosted doses or splitting the daily dose into twice-daily doses warranted investigation in ART-experienced children, adolescents, and young adults.<sup>14</sup>



**Table A. Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A**

Age Range	ATV Given with RTV	ATV Median Dose (mg/m <sup>2</sup> ) <sup>a</sup>	ATV Median Dose (mg)
6–13 years	No	509	475
6–13 years	Yes	206	200
>13 years	No	620	900
>13 years	Yes	195	350

<sup>a</sup> These doses satisfied protocol-defined area under the curve/pharmacokinetic parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. Therapeutic drug monitoring was used to determine patient-specific dosing in this trial.

Source: Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-96.

Key: ATV = atazanavir; RTV = ritonavir

In the report of the IMPAACT/PACTG P1020A data, ATV satisfied PK criteria at a dose of 205 mg per m<sup>2</sup> of body surface area in pediatric subjects when administered with RTV.<sup>12</sup> A study of a model-based approach that used ATV concentration-time data from three adult studies and one pediatric study (P1020A),<sup>15</sup> along with subsequent additional adjusted modeling,<sup>16</sup> informed the use of the following weight-based ATV/r doses that are listed in the current FDA-approved product label for children aged ≥6 to <18 years:

- Weighing 15 to <35 kg: ATV/r 200 mg/100 mg
- Weighing ≥35 kg: ATV/r 300 mg/100 mg

### **Cobicistat as a Pharmacokinetic Enhancer**

COBI (as Tybost) is approved by the FDA at the 150-mg dose for use with ATV 300 mg in children and adolescents weighing ≥35 kg. A study of 14 adolescents, aged 12 to 18 years, showed that COBI is a safe and effective PK enhancer when used in combination with ATV and two NRTIs in adolescent patients.<sup>17</sup> PK findings from this study are summarized in [Table B](#) below.

**Table B. Pharmacokinetic Parameters for Atazanavir Administered with Cobicistat (as Tybost) in Pediatric Patients Aged 12 to 18 Years and Adults**

PK Parameters <sup>a</sup>	ATV		COBI	
	Pediatric Patients (n = 12)	Adult Patients (n = 30)	Pediatric Patients (n = 12)	Adult Patients (n = 30)
AUC <sub>tau</sub> µg·h/mL Geometric mean (CV%)	49.48 (49.1)	39.96 (52.1)	12.11 (44.7)	9.65 (41.8)
C <sub>max</sub> µg/mL Geometric mean (CV%)	4.32 (49.9)	3.54 (45.8)	1.28 (31.7)	1.28 (35.6)
C <sub>tau</sub> µg/mL Geometric mean (CV%)	0.91 (96.4)	0.58 (84.7)	0.09 (156.2)	0.04 (112.7)

<sup>a</sup> The information in this table comes from the Tybost package insert.<sup>10</sup>

**Key:** ATV = atazanavir; AUC<sub>tau</sub> = area under the concentration-time curve over the dosing interval; C<sub>max</sub> = maximum serum concentration; C<sub>tau</sub> = trough serum concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; PK = pharmacokinetic

## Oral Powder

The unboosted ATV powder arms in IMPAACT/PACTG P1020A were closed, because participants were unable to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets (30,000 ng·hr/mL to 90,000 ng·hr/mL) were established based on exposures in adults in early studies of unboosted ATV. In IMPAACT/PACTG P1020A, children aged 3 months to 2 years who were in the boosted ATV powder cohorts and who received a daily dose of ATV 310 mg per m<sup>2</sup> of body surface area achieved average ATV exposures that approached, but did not meet, protocol targets. Variability in exposures was high, especially among the very young children of 3 months to 2 years in this study.<sup>8</sup>

Assessment of the PK, safety, tolerability, and virologic response of ATV oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE-1, which enrolled pediatric patients aged 3 months to <6 years<sup>9</sup>
- PRINCE-2, which enrolled pediatric patients aged 3 months to <11 years<sup>10</sup>

In total, 134 treated patients (weighing 5 to <35 kg) from both studies were evaluated during the FDA approval process. All patients in the PRINCE trials were treated with boosted ATV and two NRTIs. Children received an oral solution that contained ATV and RTV. Doses were assigned according to the child's weight:

- Weighing 5 to <10 kg: ATV 150 mg or ATV 200 mg and RTV 80 mg
- Weighing 10 to <15 kg: ATV 200 mg and RTV 80 mg
- Weighing 15 to <25 kg: ATV 250 mg and RTV 80 mg
- Weighing 25 to <35 kg: ATV 300 mg and RTV 100 mg

No new safety concerns were identified during these trials. [Table C](#) lists the PK parameters that were measured during the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses.

**Table C. Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE-1 and PRINCE-2) versus Capsules in Young Adults and Adults**

PK Parameters	PRINCE Trial <sup>a</sup> ATV/r					Young Adult Study <sup>b</sup>	Adult Study
	Dose: 150 mg/80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/80 mg Weighing: 10 kg to <15 kg	Dose: 250 mg/80 mg Weighing: 15 kg to <25 kg	Dose: 300 mg/100 mg Weighing: ≥25 kg to <35 kg		
AUC ng·h/mL Mean <sup>c</sup> (CV% or 95% CI)	32,503 (61) n = 20	39,519 (54) n = 10	50,305 (67) n = 18	55,687 (45) n = 31	44,329 (63) n = 8	35,971 (30,853–41,898) n = 22	46,073 (66) n = 10
C <sub>24h</sub> ng/mL Mean <sup>c</sup> (CV% or 95% CI)	336 (76) n = 20	550 (60) n = 10	572 (111) n = 18	686 (68) n = 31	468 (104) n = 8	578 (474–704) n = 22	636 (97) n = 10

<sup>a</sup> This information comes from the Reyataz package insert.<sup>10</sup>

<sup>b</sup> The young adults also were receiving tenofovir disoproxil fumarate.<sup>7</sup>

<sup>c</sup> Means are geometric means.

**Note:** RTV oral solution is no longer available. Use of ATV/r is now limited to children weighing ≥15 kg who can receive 100 mg RTV using powder or tablets.

**Key:** ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation; PK = pharmacokinetic

In these PK studies, although the PK targets were met in all patients using ATV powder except those who received ATV/r 150 mg/80 mg in the 5 to <10 kg weight band, the coefficients of variation were large, especially among the youngest patients.

### Transitioning from Powder to Capsules

For children who reach a weight ≥25 kg while taking the powder, ATV 300 mg-powder (six packets) plus RTV 100-mg oral solution, both administered once daily with food, may be used. ATV capsules should be used for children who can swallow pills. Bioavailability is higher for the capsules than for the powder; therefore, a lower mg/kg dose is recommended when using capsules. Opened capsules have not been studied and should not be used.

### Toxicity

In the IMPAACT/PACTG 1020A trial, 9% of patients enrolled had a total bilirubin ≥5.1 times the upper limit of normal,<sup>12</sup> whereas 9% of patients enrolled in the PRINCE studies had a total bilirubin ≥2.6 times the upper limit of normal.<sup>9,11</sup> The most common laboratory abnormality during the

PRINCE trials was elevated amylase levels, which occurred in 33% of patients.<sup>10</sup> Three children (2%) had treatment-related cardiac disorders during the PRINCE trials; one child discontinued therapy because of QT corrected for heart rate (QTc) prolongation, and two experienced first-degree AV block.<sup>9,11</sup> In IMPAACT/PACTG P1020A, three children (3%) had QTc prolongations >470 msec; two of these children came off the study, and all were asymptomatic.

## Darunavir (DRV, Prezista)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Oral Suspension: 100 mg/mL</p> <p>Tablets: 75 mg, 150 mg, 600 mg, 800 mg</p> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>[Prezcobix] Darunavir 800 mg/cobicistat 150 mg</li> <li>[Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Note:</b> Darunavir (DRV) should not be used without a pharmacokinetic enhancer (boosting agent). Ritonavir (RTV) may be used as the boosting agent in children and adults. Cobicistat (COBI) may be used as a boosting agent with DRV in children weighing <math>\geq 40</math> kg and in adults.</p> <p><b>Neonate/Infant Dose</b></p> <ul style="list-style-type: none"> <li>DRV is not approved for use in neonates/infants.</li> </ul> <p><b>Child Dose</b></p> <p><i>Aged &lt;3 Years</i></p> <ul style="list-style-type: none"> <li><b>Do not use DRV in children aged &lt;3 years or weighing <math>\leq 10</math> kg.</b> In juvenile rats, DRV caused convulsions and death; these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.</li> </ul> <p><i>Aged <math>\geq 3</math> to &lt;12 Years</i></p> <ul style="list-style-type: none"> <li>Dosing recommendations in the table below are for children aged <math>\geq 3</math> to &lt;12 years and weighing <math>\geq 20</math> kg who are antiretroviral therapy-naïve or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with DRV resistance.</li> </ul>	<ul style="list-style-type: none"> <li>Skin rash, including Stevens-Johnson syndrome and erythema multiforme</li> <li>Hepatotoxicity</li> <li>Diarrhea, nausea</li> <li>Headache</li> <li>Hyperlipidemia, transaminase elevation, hyperglycemia</li> <li>Fat maldistribution</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>Once-daily DRV is not generally recommended for use in children aged &lt;12 years or weighing &lt;40 kg. Dosing estimates for these patients were based on limited data, and limited clinical experience exists with this dosing schedule in this age group.</li> <li>Once-daily DRV <b>should not be used</b> if any one of the following resistance-associated mutations is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.</li> <li><b>DRV must be administered with food</b>, which increases DRV plasma concentrations by about 30%.</li> <li>DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.</li> </ul>

**Twice-Daily DRV and RTV Doses for Children Aged 3 to <12 Years and Weighing  $\geq 20$  kg**

Weight	Dose (Twice Daily with Food) <sup>a</sup>
20 kg to <30 kg <sup>b</sup>	DRV 375 mg (combination of tablets or 3.8 mL) <sup>d</sup> plus RTV 100 mg (tablet or powder) <sup>e</sup>
30 kg to <40 kg <sup>b</sup>	DRV 450 mg (combination of tablets or 4.6 mL) <sup>d</sup> plus RTV 100 mg (tablet or powder)
$\geq 40$ kg <sup>b</sup>	DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or powder)

**Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 30$  to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients with or without at Least One Mutation Associated with DRV Resistance**

- DRV 450 mg (using a combination of tablets) plus RTV 100 mg, both twice daily with food

**Child and Adolescent (Aged  $\geq 12$  years and Weighing  $\geq 40$  kg)<sup>d</sup> and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with DRV Resistance**

- DRV 800 mg (using a tablet or combination of tablets) plus RTV 100 mg, both once daily with food

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with DRV Resistance**

- DRV 800 mg (tablet) plus COBI<sup>e</sup> 150 mg (tablet) or the coformulation Prezcoibix, once daily with food

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with DRV Resistance**

- DRV 600 mg plus RTV 100 mg, both twice daily with food
- The use of COBI is **not recommended** with DRV 600 mg twice daily.

**[Prezcoibix] DRV/COBI**

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with DRV Resistance*

- One tablet once daily with food

**[Symtuza] DRV/COBI/Emtricitabine (FTC)/ Tenofovir Alafenamide (TAF)**

- Pediatric dosing requires coadministration of tablets of different strengths to achieve the recommended dose for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.
- Store DRV tablets and oral suspension at room temperature (25° C or 77° F). The suspension must be shaken well before dosing.
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain FTC or TAF. Severe acute exacerbation of HBV infection can occur when FTC or TAF are discontinued; therefore, liver function should be monitored for several months after patients with HBV infection stop taking FTC or TAF.

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor

**DRV Dosing in Patients with Hepatic Impairment**

- DRV is primarily metabolized by the liver. Caution should be used when administering DRV to patients with hepatic impairment. DRV is **not recommended** in patients with severe hepatic impairment.

**DRV Dosing in Patients with Renal Impairment**

- No DRV dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).
- The FDC Symtuza is **not recommended** for use in patients with an estimated CrCl <30 mL/min.

#### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose

- One tablet once daily with food in ARV-naïve patients or in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no known mutations associated with resistance to DRV or tenofovir.

<sup>a</sup> Once-daily dosing of DRV is approved by the U.S. Food and Drug Administration (FDA), but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not generally recommend using this dosing schedule in children (see Frequency of Administration below).

<sup>b</sup> RTV oral solution is no longer available. Use of DRV boosted with ritonavir (DRV/r) is now limited to children weighing  $\geq 20$  mg who can receive 100 mg RTV using powder or tablets.

<sup>c</sup> The volumes for the 375-mg and 450-mg DRV doses are rounded for dosing convenience of suspension.

<sup>d</sup> Some Panel members recommend using the FDA-approved dose of once-daily DRV 675 mg (administered using a combination of tablets) plus RTV 100 mg once daily for adolescents weighing  $\geq 30$  to  $< 40$  kg (see [Table B](#) below).

<sup>e</sup> See [Cobicistat](#) for important information about toxicity, drug interactions, and monitoring in patients who receive COBI.

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- **Metabolism:** Darunavir (DRV) is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir (RTV) and cobicistat (COBI) are inhibitors of CYP3A4, thereby increasing the plasma concentration of DRV. Coadministration of DRV plus RTV (DRV/r) or DRV plus COBI (DRV/c) with drugs that are highly dependent on CYP3A clearance creates potential for multiple drug–drug interactions and may be associated with suboptimal efficacy or serious and/or life-threatening events.
- Coadministration of several drugs, including other protease inhibitors and rifampin, is **contraindicated** with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine (ETR) may reduce serum DRV concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.<sup>1</sup> Before administering DRV with a pharmacokinetic (PK) enhancer (boosting agent), a patient’s medication profile should be carefully reviewed for potential drug interactions.
  - When twice-daily DRV/r was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients aged 13 to 16 years with HIV, both TDF and DRV exposures were lower than those found in adults treated with the same combination.<sup>2</sup> No dose adjustment is recommended when using DRV/r with TDF, but caution is advised and therapeutic drug monitoring (TDM) may be useful.<sup>3</sup> Data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily ETR in children, adolescents, and young adults aged 9 to  $< 24$  years did not have a significant effect on DRV plasma concentrations.<sup>4</sup> When DRV/r was coadministered with ETR twice daily in pediatric patients, target concentrations for both DRV and ETR were achieved.<sup>5</sup> DRV PKs were not affected when DRV was coadministered with rilpivirine (RPV) in a study of adolescents and young adults.<sup>6</sup> DRV/r coadministration increased RPV exposure twofold to threefold; close monitoring for RPV-related adverse events is advisable.



## Major Toxicities

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome ; fever and elevated levels of hepatic transaminases; lipid abnormalities; and crystalluria.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in people with hemophilia, and hepatic dysfunction, particularly in patients with underlying risk factors, such as hepatitis B or hepatitis C virus coinfection.

## 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*

DRV/r is approved by the U.S. Food and Drug Administration (FDA) as a component of antiretroviral (ARV) therapy in treatment-naïve and treatment-experienced children aged  $\geq 3$  years. . Because RTV oral solution is no longer commercially available, use of DRV/r is limited to children weighing  $\geq 20$  kg who can use the RTV 100 mg powder packet or 100 mg tablet.

DRV is approved by the FDA to be administered with COBI (Tybost) boosting in pediatric patients weighing  $\geq 40$  kg. The fixed-dose combinations (FDCs) DRV/c (Prezcobix) and DRV/c/emtricitabine/tenofovir alafenamide (Symtuza) are also approved by the FDA for use in pediatric patients weighing  $\geq 40$  kg.

### *Efficacy in Clinical Trials*

In an international, multisite clinical trial (TMC114-TiDP29-C228) that enrolled treatment-experienced children aged 3 to  $<6$  years, 17 (81%) of 21 children who received DRV/r twice daily had viral loads  $<50$  copies/mL at Week 48.<sup>7-9</sup>

A randomized, open-label, multicenter pediatric trial<sup>9</sup> that evaluated twice-daily DRV/r among 80 treatment-experienced children aged 6 to  $<18$  years reported that 66% of patients had plasma HIV RNA  $<400$  copies/mL and 51% had HIV RNA  $<50$  copies/mL at Week 24.

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 to 12 years who had maintained HIV viral loads  $<50$  copies/mL for at least 6 months.<sup>10</sup> All but one child continued to have undetectable viral loads during a median of 11.6 months of follow-up (range 0.5–14.2 months). The remaining child had detectable viral load measurements between 20 copies/mL and 200 copies/mL on three occasions during a 3-month period before, again, becoming undetectable without a change in regimen.

In one study, 12 participants aged 12 to 17 years received DRV/r once daily.<sup>11</sup> After 48 weeks, all but one participant had viral loads <50 copies/mL.

## Pharmacokinetics and Dosing

### *Pharmacokinetics in Children Aged 3 to <6 Years*

Twenty-one children aged 3 to <6 years and weighing 10 to <20 kg received twice-daily DRV/r oral suspension. These children had experienced virologic failure on their previous ARV regimens and had fewer than three DRV resistance mutations, confirmed by genotypic testing.<sup>7,8,12</sup> The DRV area under the curve from 0-12 hours ( $AUC_{0-12h}$ ), measured as a percent of the adult AUC value,<sup>7,8,13</sup> was 126% overall, 143% in children weighing 10 to <15 kg, and 121% in children weighing 15 to <20 kg.

### *Pharmacokinetics in Children Aged $\geq$ 6 Years*

Initial pediatric PK evaluation of DRV tablets and RTV oral solution or tablets was based on a Phase 2 randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 to <18 years and weighing  $\geq$ 20 kg.<sup>14</sup> Part 1 of the trial used a weight-adjusted dose of DRV (9–15 mg/kg) and RTV (1.5–2.5 mg/kg) twice daily, approximating the standard adult dose of DRV/r 600 mg/100 mg twice daily on a per-weight basis. This dose resulted in inadequate drug exposure in the pediatric population studied, with a 24-hour AUC ( $AUC_{0-24h}$ ) that was 81% of the  $AUC_{0-24h}$  observed in adults and a predose concentration ( $C_{0h}$ ) that was 91% of the  $C_{0h}$  observed in adults. A pediatric dose that was 20% to 33% higher than the directly scaled adult dose was needed to achieve a drug exposure that was similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was DRV 11 to 19 mg/kg and RTV 1.5 to 2.5 mg/kg twice daily. This dose resulted in a DRV  $AUC_{0-24h}$  of 123.3 mcg•h/mL (range 71.9–201.5 mcg•h/mL) and a  $C_{0h}$  of 3,693 ng/mL (range 1,842–7,191 ng/mL), representing 102% and 114% of the respective values in adults. Doses were given twice daily and were stratified into body-weight bands of 20 to <30 kg and 30 to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 to <40 kg were selected using the findings from the safety and efficacy portion of this study (see [Table A](#) below).

A small study that involved 12 treatment-experienced children aged 6 to 12 years examined the PK and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine.<sup>10</sup> All participants had maintained HIV plasma viral loads <50 copies/mL for at least 6 months prior to beginning this regimen. The weight-based doses used for once-daily DRV/r were based on a prior modeling study<sup>15</sup>: 600 mg/100 mg for patients weighing 15 to 30 kg, 675 mg/100 mg for patients weighing 30 to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The geometric mean  $AUC_{0-24h}$  was below the study target of 80% of the value seen in adults (63.1 mg•h/L vs. 71.8 mg•h/L), but the trough values that were observed at 23.1 hours to 25.1 hours after the previous dose exceeded the trough plasma concentration recommended for treatment-experienced adults (0.55 mg/L).<sup>16</sup> One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to DRV; the  $AUC_{0-24h}$  was 47.8 mg•h/L.

**Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Background Therapy in Children, Adolescents, and Adults**

Population	n	Dose of DRV/r	AUC <sub>12h</sub> (mcg·h/mL) Median <sup>a</sup>	C <sub>0h</sub> (ng/mL) Median <sup>a</sup>
Children Weighing 10 kg to <15 kg <sup>a</sup>	13	20 mg/kg/3 mg/kg	66.0	3,533
Children Weighing 10 kg to <15 kg <sup>a</sup>	4	25 mg/kg/3 mg/kg	116.0	8,522
Children Weighing 15 kg to <20 kg <sup>a</sup>	11	20 mg/kg/3 mg/kg	54.2	3,387
Children Weighing 15 kg to <20 kg <sup>a</sup>	14	25 mg/kg/3 mg/kg	68.6	4,365
Children Aged 6 to <12 Years <sup>b</sup>	24	Determined by weight bands <sup>b</sup>	56.4	3,354
Adolescents Aged 12 to <18 Years <sup>b</sup>	50	Determined by weight bands <sup>b</sup>	66.4	4,059
Adults Aged >18 Years <sup>c</sup> (Three Studies)	285/278/119	600 mg/100 mg	54.7–61.7	3,197–3,539

<sup>a</sup> Source: U.S. Food and Drug Administration. FDA clinical pharmacologic review of darunavir. 2011. Available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf>.

<sup>b</sup> DRV/r was administered at doses of 375 mg/50 mg twice daily for patients weighing 20 to <30 kg, 450 mg/60 mg twice daily for patients weighing 30 to <40 kg, and 600 mg/100 mg twice daily for patients weighing ≥40 kg. Data from the 2008 FDA pharmacokinetics review. Available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf>.

<sup>c</sup> Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021976s043,202895s017bledt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017bledt.pdf).

**Note:** RTV oral solution is no longer available. Use of DRV/r is now limited to children weighing ≥20 mg who can receive 100 mg RTV using powder or tablets.

Key: AUC<sub>12h</sub> = 12-hour area under the curve; C<sub>0h</sub> = predose concentration; DRV/r = darunavir/ritonavir

## Dosing

### Pharmacokinetic Enhancers

DRV should not be used without a PK enhancer (boosting agent). RTV may be used as a boosting agent in children and adults. COBI may be used as a boosting agent in children weighing ≥40 kg and adults.

A study that enrolled 19 Thai children used the RTV 100-mg capsule twice daily as the boosting dose for twice-daily DRV 375 mg (in children weighing 20 to <30 kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing ≥40 kg).<sup>17</sup> The DRV exposures with RTV 100 mg twice daily were similar to those obtained in the studies with lower (<100 mg) doses of liquid RTV.<sup>14,17</sup> The tolerability and PK data from this small study support the use of RTV 100 mg for boosting using either the powder or tablet formulation in children weighing ≥20 kg. No data are available on the safety and tolerability of using DRV with the RTV 100-mg tablet or powder formulation in children weighing <20 kg.

Data on the dosing of DRV/c are available primarily for adult patients.<sup>18</sup> Data on once-daily use of the FDC tablet DRV/c 800 mg/150 mg (Prezcobix) showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.<sup>16</sup>

In an open-label switch study, eight adolescent patients with a median age of 14 years (range 12–17 years) who received DRV/c had DRV exposures (area under the curve for the dosing interval [AUC<sub>tau</sub>]) that were similar to those observed in adults, except for a lower trough concentration at the end of the dosing interval (C<sub>tau</sub>). The median DRV C<sub>tau</sub> (494 ng/mL) was above the protein binding–adjusted half-maximal inhibitory concentration for wild-type virus (55 ng/mL). Adolescent patients in this study received the adult dose of COBI 150 mg daily. DRV dosing was based on weight, with patients who weighed ≥40 kg receiving DRV 800 mg once daily and patients who weighed 30 to <40 kg receiving DRV 675 mg once daily. In this small sample, 95.5% of patients had HIV RNA <50 copies/mL at Week 12. COBI appeared to be well tolerated with no discontinuations due to adverse events.<sup>19</sup>

### ***Frequency of Administration***

In February 2013, the FDA approved the use of once-daily DRV for treatment-naïve children and for treatment-experienced children without DRV resistance–associated mutations (see [Table B](#) below). Population PK modeling and simulation were used to develop recommendations for once-daily dosing in younger pediatric subjects aged 3 to <12 years and weighing 10 to <40 kg.<sup>8,20</sup> Currently, limited data exist on the efficacy of once-daily DRV/r dosing in treatment-naïve or treatment-experienced children aged <6 years. Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) generally recommends dosing DRV/r twice daily in children aged ≥3 to <12 years (see [Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg](#) below). The Panel recommends that once-daily DRV/r be used only in treatment-naïve and treatment-experienced adolescents weighing ≥40 kg who do not have mutations that are associated with DRV resistance. If DRV and RTV are used once daily in children aged <12 years, the Panel recommends conducting a PK evaluation of plasma concentrations of DRV and closely monitoring viral load.

**Table B. U.S. Food and Drug Administration–Approved Once-Daily Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg Who Are Treatment Naive or Treatment Experienced with No Darunavir Resistance–Associated Mutations**

**Note:** The Panel generally recommends dosing DRV plus RTV twice daily in children aged ≥3 to <12 years.

Weight	Dose (Once Daily with Food)
15 kg to <30 kg	DRV 600 mg (tablet, combination of tablets, or 6 mL) plus RTV 100 mg (tablet or powder) <sup>a</sup>
30 kg to <40 kg	DRV 675 mg (combination of tablets or 6.8 mL) <sup>b,c</sup> plus RTV 100 mg (tablet or powder) <sup>a</sup>
≥40 kg	DRV 800 mg (tablet, combination of tablets, or 8 mL) <sup>c</sup> plus RTV 100 mg (tablet or powder) <sup>a</sup>

<sup>a</sup> RTV oral solution is no longer available. Use of DRV/r is now limited to children weighing ≥20 kg who can receive 100 mg RTV using powder or tablets.

<sup>b</sup> DRV 100 mg/mL oral suspension; the 675-mg once daily DRV dose is rounded for dosing convenience of suspension.

<sup>c</sup> The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) once daily by refilling the oral dosing syringe supplied by the manufacturer or as one administration once daily if a larger syringe is provided by a pharmacy or provider.

Key: DRV = darunavir; DRV/r = darunavir/ritonavir; RTV = ritonavir

**Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg**

During the TMC114-C228 trial, the researchers investigated once-daily dosing of DRV for 2 weeks; DRV PK were evaluated in treatment-experienced children aged 3 to <12 years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen.<sup>16,20</sup> The DRV/r dose for once-daily use, which was based on PK simulation and did not include a relative bioavailability factor, was DRV 40 mg/kg coadministered with approximately 7 mg/kg of RTV for children weighing <15 kg and DRV/r 600 mg/100 mg once daily for children weighing ≥15 kg.<sup>20,21</sup> The PK data obtained from 10 children aged 3 to 6 years in this substudy (see [Table C](#) below) were included as part of the population PK modeling and simulation that was used to determine the FDA-approved dose for once-daily DRV/r in children aged 3 to <12 years.

In a small study in which DRV/r was administered once daily to 12 treatment-experienced children aged 6 to 12 years,<sup>10</sup> the geometric mean AUC<sub>0–24h</sub> achieved was below the study target of 80% of the value seen in adults (63.1 mg•h/L vs. 71.8 mg•h/L). Trough values exceeded the plasma concentration that is recommended for treatment-experienced patients (0.55 mg/L). Despite the FDA dosing guidelines, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 to <12 years. The Panel makes this recommendation because of the small data set used for once-daily DRV/r PK modeling and the limited amount of data on the use of once-daily DRV/r in children aged <12 years.

**Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Background Therapy**

PK Parameter	Children Aged 3 to 6 Years (n = 10) <sup>a</sup>	Adults (n = 335)
DRV AUC <sub>0-24h</sub> geometric mean, ng•h/mL (SD)	115 (40.6)	89.7 (27.0)
DRV C <sub>0h</sub> geometric mean, ng/mL (SD)	3,029 (1,715)	2,027 (1,168)

<sup>a</sup> Source: Kakuda TN, Brochot A, van de Castele T, et al. Establishing darunavir dosing recommendations in treatment-naive and treatment-experienced pediatric patients. Presented at: 14th Clinical Pharmacology Workshop on HIV; 2013. Amsterdam, Netherlands. Available at: [https://www.natap.org/2013/Pharm/Pharm\\_19.htm](https://www.natap.org/2013/Pharm/Pharm_19.htm).

Key: AUC<sub>0-24h</sub> = 24-hour area under the curve; C<sub>0h</sub> = predose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

### Once-Daily Administration in Adolescents Aged ≥12 Years and Weighing ≥40 kg

A substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that DRV exposures in 12 treatment-naive adolescents (aged 12–17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily DRV (see [Table D](#) below).<sup>11</sup> After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL.<sup>11</sup> Interestingly, no relationship was observed between DRV AUC<sub>0-24h</sub> and C<sub>0h</sub> and virologic outcome (HIV RNA <50 copies/mL) in this study. DRV exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of DRV/r 800 mg/100 mg was administered to 24 subjects with a median age of 19.5 years (range 14–23 years).<sup>22</sup> However, DRV exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting that higher doses may be needed in younger adolescents. A single case report involving a highly treatment-experienced adolescent patient suggests that using an increased DRV dose with standard RTV boosting and employing TDM can lead to virologic suppression.

**Table D. Darunavir Pharmacokinetics with Once-Daily Administration in Adolescents Aged ≥12 Years and Adults Aged >18 Years**

Population	n	Dose of DRV/r	AUC <sub>0-24h</sub> <sup>a</sup> (mcg•h/L) Median	C <sub>0h</sub> (ng/mL) Median
Adolescents Aged 12–17 Years (Mean Age 14.6 years) <sup>b</sup>	12	800 mg/100 mg	86.7	2,141
Adolescents and Adults Aged 14–23 Years (Mean Age 19.5 years) <sup>c</sup>	24	800 mg/100 mg	69.5	1,300
Adults Aged >18 Years (Two Studies) <sup>a</sup>	335/280	800 mg/100 mg	87.8–87.9	1,896–2,041

<sup>a</sup> Source: Darunavir [package insert]. Food and Drug Administration. 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/021976Orig1s063lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021976Orig1s063lbl.pdf).

<sup>b</sup> Source: Kakuda TN, Brochot A, van de Castele T, et al. Establishing darunavir dosing recommendations in treatment-naive and treatment-experienced pediatric patients. Presented at: 14th Clinical Pharmacology Workshop on HIV; 2013. Amsterdam, Netherlands. Available at: [https://www.natap.org/2013/Pharm/Pharm\\_19.htm](https://www.natap.org/2013/Pharm/Pharm_19.htm).

© Source: Flynn P, Blanche S, Giaquinto C, et al. . 24-week efficacy, safety, tolerability and pharmacokinetics of darunavir/ritonavir once daily in treatment-naïve adolescents aged 12 to < 18 years in DIONE. Abstract # PP\_2. Presented at: 3rd International Workshop on HIV Pediatrics; 2011. Rome, Italy. Available at: [https://www.natap.org/2011/IAS/IAS\\_40.htm](https://www.natap.org/2011/IAS/IAS_40.htm).

**Key:**  $AUC_{0-24h}$  = 24-hour area under the curve;  $C_{0h}$  = predose concentration; DRV/r = darunavir/ritonavir

The efficacy of once-daily DRV has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.<sup>11,23</sup>



## Lopinavir/Ritonavir (LPV/r, Kaletra)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Oral Solution</b></p> <ul style="list-style-type: none"> <li>[Kaletra] Lopinavir 80 mg/mL and ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)</li> </ul> <p><b>Film-Coated Tablets</b></p> <ul style="list-style-type: none"> <li>[Kaletra] Lopinavir 100 mg/ritonavir 25 mg</li> <li>[Kaletra] Lopinavir 200 mg/ritonavir 50 mg</li> </ul> <p>When using fixed-dose combination (FDC) tablets, refer to other sections of the <a href="#">Drug Appendix</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Neonate (Aged &lt;14 Days) Dose</b></p> <ul style="list-style-type: none"> <li>Lopinavir/ritonavir (LPV/r) is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.</li> </ul> <p><b>Dosing for Individuals Who Are Not Receiving Concomitant Nevirapine (NVP), Efavirenz (EFV), Fosamprenavir (FPV), or Nelfinavir (NFV)</b></p> <p><i>Infant (Aged 14 Days to 12 Months) Dose</i></p> <ul style="list-style-type: none"> <li>Once-daily dosing is <b>not recommended</b>.</li> <li>LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. Use of this dose in infants aged &lt;12 months is associated with lower lopinavir (LPV) trough levels than those found in adults; LPV dosing should be adjusted for growth at frequent intervals (see Pharmacokinetics and Dosing below).</li> </ul> <p><i>Child and Adolescent (Aged &gt;12 Months to 18 Years) Dose</i></p> <ul style="list-style-type: none"> <li>Once-daily dosing is <b>not recommended</b>.</li> <li>LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing &lt;15 kg, this dose</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, alteration of taste</li> <li>Hyperlipidemia, especially hypertriglyceridemia</li> <li>Elevated transaminases</li> <li>Hyperglycemia</li> <li>PR interval prolongation</li> <li>QT interval prolongation and Torsades de Pointes</li> <li>Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.</li> <li>LPV/r tablets must be swallowed whole. <b>Do not crush or split tablets.</b></li> <li>LPV/r oral solution should be administered with food because a high-fat meal increases absorption.</li> </ul>

approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing  $\geq 15$  kg to 45 kg, this dose approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for antiretroviral therapy (ART)–experienced patients who could harbor virus with decreased LPV susceptibility (see Pharmacokinetics and Dosing below).

- LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged  $>1$  year. For patients weighing  $<15$  kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing  $\geq 15$  kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose **should not be used** in treatment-experienced patients who could harbor virus with decreased LPV susceptibility.

**Weight-Band Dosing for LPV/r 100-mg/25-mg Pediatric Tablets in Children and Adolescents**

Recommended Number of LPV/r 100-mg/25-mg Tablets Given Twice Daily		
Dosing target	300 mg/m <sup>2</sup> per dose given twice daily	230 mg/m <sup>2</sup> per dose given twice daily
Body Weight		
15 kg to 20 kg	2	2
$>20$ kg to 25 kg	3	2
$>25$ kg to 30 kg	3	3
$>30$ kg to 35 kg	4 <sup>a</sup>	3
$>35$ kg to 45 kg	4 <sup>a</sup>	4 <sup>a</sup>
$>45$ kg	4 <sup>a</sup> or 5 <sup>b</sup>	4 <sup>a</sup>

<sup>a</sup> Two tablets that each contain LPV/r 200 mg/50 mg can be substituted for the four LPV/r 100-mg/25-mg tablets in children who are capable of swallowing a larger tablet.

<sup>b</sup> In patients who weigh  $>45$  kg and who are receiving concomitant NVP, EFV, FPV, or NFV, the FDA-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

**Adult (Aged  $\geq 18$  Years) Dose**

- LPV/r 800 mg/200 mg once daily; *or*
- LPV/r 400 mg/100 mg twice daily

- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Formulations below).
- LPV/r oral solution can be kept at room temperature (up to 77°F or 25°C) if used within 2 months. If kept refrigerated (36°F to 46°F or 2°C to 8°C), LPV/r oral solution remains stable until the expiration date printed on the label.
- Children aged  $<18$  years who receive once-daily dosing of LPV/r have shown considerable variability in plasma concentrations and have a higher incidence of diarrhea. Therefore, once-daily dosing **is not recommended** for this age group.
- Use of LPV/r once daily is **contraindicated** if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher LPV trough concentrations may be required to suppress resistant virus.

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor.

**LPV/r Dosing in Patients with Hepatic Impairment**

- LPV/r is eliminated primarily by hepatic metabolism. Use caution when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. Ritonavir inhibits the metabolism of LPV and increases LPV plasma concentrations.

- Do not use once-daily dosing in children; adolescents; patients receiving concomitant therapy with NVP, EFV, FPV, or NFV; or patients with three or more LPV-associated mutations (see Special Instructions for a list of mutations below).

**Dosing for Individuals with Three or More LPV-Associated Mutations (See Special Instructions for List)**

- LPV/r 400 mg/100 mg twice daily

**Dosing for Individuals Receiving Concomitant NVP or EFV**

- These drugs induce LPV metabolism and reduce LPV plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing **should not be used** in these patients.

*Child and Adolescent (Aged >12 Months to  $\leq$  18 Years) Dose*

- LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily. See the table above for weight-band dosing when using tablets.

*Adult (Aged  $\geq$  18 Years) Dose*

- The FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing **should not be used**.

**LPV/r Used in Combination with Maraviroc**

- Maraviroc doses may need modification (see the [Maraviroc](#) section).

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Lopinavir/ritonavir (LPV/r) is a cytochrome P450 (CYP) 3A4 substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease LPV plasma concentrations, whereas coadministering LPV/r with other CYP3A4 inhibitors may increase LPV plasma concentrations. Coadministering LPV/r with other CYP3A4 substrates may require dose adjustments and additional monitoring.

Before initiating therapy with LPV/r, a patient's medication profile should be carefully reviewed for potential drug interactions. In patients treated with LPV/r, fluticasone (a commonly used inhaled and intranasal steroid) should be avoided, and an alternative steroid should be used. **Fluticasone is a CYP3A substrate and LPV/r significantly increases fluticasone exposures, potentially resulting in adverse systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.**<sup>1</sup> Drug interactions with antituberculous drugs are common. Coadministration of LPV/r with the antituberculosis drug rifampin—a strong CYP3A4 inducer—may lead to suboptimal LPV levels.<sup>2-4</sup>

Patients who are receiving both LPV/r and antituberculous drugs may need a dose adjustment for LPV/r, or they may need to switch to an antiretroviral (ARV) regimen that does not include LPV/r.

## Major Toxicities

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance,<sup>5</sup> and hyperlipidemia, especially hypercholesterolemia and hypertriglyceridemia,<sup>6-8</sup> which may be more pronounced in girls than in boys.<sup>9</sup> LPV requires a higher dose of ritonavir than some other protease inhibitors (PIs); this higher dose may exacerbate these adverse events (AEs).
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, hepatitis (which has been life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur<sup>10</sup>.
- *Special populations—neonates:* An increased risk of toxicity in premature infants has been reported, including cases of transient symptomatic adrenal insufficiency,<sup>11,12</sup> life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),<sup>13-15</sup> lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be caused by the drug itself and/or by the inactive ingredients in the oral solution,<sup>15</sup> which include propylene glycol (15.3%) and ethanol (42.4%). Transient asymptomatic elevation in 17-hydroxyprogesterone levels also has been reported<sup>11</sup> in term newborns treated at birth with LPV/r. The pharmacokinetics (PK) and safety of LPV/r were studied in IMPAACT P1106, a Phase 4 prospective study evaluating the safety and PK of antiretroviral medications in low and normal birthweight infants <3 months old, in which one group received LPV/r as clinical care<sup>16</sup>. A total of 28 neonates with HIV were enrolled, with a median birth weight of 2,288 g (interquartile range [IQR] 1,360–3,320 g) and a median gestational age of 36 weeks (IQR 27–39 weeks). In 25 infants with available PK data, the median LPV dose was 418mg/m<sup>2</sup> twice daily (23.6 mg/kg). The median trough LPV levels was 5.14 (IQR 2.95–8.51) µg/mL, above the minimal effective target concentration of 1 µg/mL. Nearly half of infants initiated therapy prior to 42 weeks postmenstrual age with no observed safety or PK differences compared with infants who initiated LPV/r at or after 42 weeks postmenstrual age. No adverse events Grade 3 or higher were considered related to LPV/r treatment.<sup>16</sup>

## Resistance

The International Antiviral Society–USA maintains a list of [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

LPV/r is approved by the U.S. Food and Drug Administration (FDA) for use in children, including neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. The potential benefit of using LPV/r in premature infants who have not met these age thresholds must be carefully balanced with the risk of metabolic and cardiac toxicity. In pediatric patients

receiving LPV/r at a dose of 300 mg/75 mg per m<sup>2</sup> twice daily, lower LPV exposure has been observed in infants aged <6 weeks relative to older children.<sup>17</sup>

## ***Efficacy***

Clinical trials involving antiretroviral therapy (ART)–naïve adults have shown that regimens that contain LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens, including regimens that contain atazanavir, darunavir (DRV), fosamprenavir (FPV), saquinavir/ritonavir, or efavirenz (EFV). Studies also have shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that contain nelfinavir (NFV) and inferior to regimens that contain DRV.<sup>18-26</sup>

LPV/r has been studied in both ART-naïve and ART-experienced children and has demonstrated durable virologic activity and acceptable toxicity.<sup>27-35</sup>

## **Pharmacokinetics**

### ***General Considerations***

Children have lower LPV/r exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the typical adult body surface area of 1.73 m<sup>2</sup>. For the adult dose of LPV/r 400 mg/100 mg, the scaled pediatric dose would be approximately LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area. However, younger children have higher LPV clearance and need higher doses to achieve LPV exposures that are similar to those seen in adults treated with standard doses. To achieve a trough concentration (C<sub>trough</sub>) similar to that observed in adults, the pediatric dose needs to be increased 30% greater than the dose that is directly scaled for body surface area. LPV exposures in infants<sup>17,29,34</sup> are compared to those in older children<sup>27</sup> and adults<sup>36</sup> in [Table A](#) below.

**Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age**

PK Parameters	Adults (n = 19) <sup>36</sup>	Children (n = 12) <sup>27</sup>	Children (n = 15) <sup>27</sup>	Infants <sup>a</sup> at 12 Months (n = 20) <sup>34</sup>	Infants at 6 Weeks to 6 Months (n = 18) <sup>29</sup>	Infants at 14 Days to <6 Weeks (n = 9) <sup>17</sup>
LPV Dose	400 mg	230 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>
AUC <sub>0-12</sub> (mcg·hr/mL)	92.6	72.6	116.0	101.0	74.5	43.4
C <sub>max</sub> (mcg/mL)	9.8	8.2	12.5	12.1	9.4	5.2
C <sub>trough</sub> (mcg/mL)	7.1	4.7	7.9	4.9	2.7	2.5
C <sub>min</sub> (mcg/mL)	5.5	3.4	6.5	3.8	2.0	1.4

<sup>a</sup> This column contains unreported data that were originally generated for a published study. The data were provided by Edmund Capparelli, Pharm.D., in a personal communication (April 18, 2012).

**Note:** Values are means, and PK parameters refer to the LPV component; all data come from studies wherein none of the participants received non-nucleoside reverse transcriptase inhibitors as part of their antiretroviral therapy.

Key: AUC<sub>0-12h</sub> = area under the curve from time zero to 12 hours after drug administration; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; C<sub>trough</sub> = trough concentration; LPV = lopinavir; m = meter; mcg = microgram; mg = milligram; mL = milliliter; PK = pharmacokinetic

Models suggest that diet, body weight, and postnatal age are important factors in LPV PKs, with higher bioavailability as dietary fat increases during the first year of life<sup>37</sup> and clearance slowing by age 2.3 years.<sup>38</sup> A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per m<sup>2</sup> of body surface area per dose or 300 mg per m<sup>2</sup> of body surface area per dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. The findings suggested that the higher dose was associated with improved long-term viral load suppression.<sup>39</sup>

## Pharmacokinetics and Dosing

### *14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

The PKs of the oral solution at approximately LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily were evaluated in infants aged <6 weeks<sup>17</sup> and infants aged 6 weeks to 6 months.<sup>29</sup> Even at this higher dose, C<sub>trough</sub> levels were highly variable, but they were lower in infants than in children aged >6 months. C<sub>trough</sub> levels were lower in infants aged ≤6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, LPV area under the curve (AUC) was similar to that found in older children.<sup>34</sup> Because infants grow rapidly in the first months of life, it is important to optimize LPV dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per m<sup>2</sup> of body surface area in older children and adolescents,<sup>30</sup> some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg per m<sup>2</sup> of body surface area dose to allow for projected growth between clinic appointments.

### *12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

Lower C<sub>trough</sub> values have been observed in children receiving LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily than in children receiving LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (see [Table A](#) above).<sup>26</sup> Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (when LPV/r is given without nevirapine [NVP], EFV, FPV, or NFV), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily, immediate dose reduction at age 12 months **is not recommended**; many practitioners would allow patients to “grow into” the dose of LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily as they gain weight over time. Some practitioners would continue the infant dose (LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily) while using the LPV/r liquid formulation.



## Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

In both children and adults, the LPV  $C_{\text{trough}}$  is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant FPV or NFV. Higher doses of LPV are recommended when the drug is given in combination with NVP, EFV, FPV, or NFV. In 14 children who were treated with LPV/r 230 mg/57.5 mg per  $\text{m}^2$  of body surface area per dose twice daily plus NVP,<sup>27</sup> the mean LPV  $C_{\text{trough}}$  was  $3.77 \pm 3.57$  mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, but the variability in concentration is much higher in children than in adults.<sup>27,40</sup> In a study of 15 children with HIV aged 5.7 to 16.3 years who were treated with LPV/r 300 mg/75 mg per  $\text{m}^2$  of body surface area per dose twice daily plus EFV 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in LPV  $C_{\text{trough}}$  values. Five of 15 children (33%) had LPV 12-hour  $C_{\text{trough}}$  values that were  $<1.0$  mcg/mL, the plasma concentration needed to inhibit wild-type HIV.<sup>41</sup> A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/75 mg per  $\text{m}^2$  of body surface area twice daily plus EFV 350 mg per  $\text{m}^2$  of body surface area once daily reported only one patient (6.6%) with subtherapeutic LPV  $C_{\text{trough}}$  values,<sup>42</sup> perhaps because the trial used an EFV dose that was approximately 11 mg/kg body weight<sup>42</sup> instead of the 14 mg/kg body weight dose used in the trial discussed above.<sup>41</sup>

## Dosing

### *Once Daily*

A single daily dose of LPV/r 800 mg/200 mg is approved by the FDA for treatment of HIV in treatment-naïve adults aged  $>18$  years. However, once-daily administration **cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM)**; once-daily administration may be successful in select, closely monitored children.<sup>43</sup> There is high interindividual variability in drug exposure for LPV/r, and trough plasma concentrations may fall below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naïve children and adolescents.<sup>44-47</sup> The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.<sup>47,48</sup> An international, randomized, open-label trial attempted to demonstrate that once-daily LPV/r dosing was non-inferior to twice-daily LPV/r dosing in children and adolescents with HIV. This trial was unsuccessful, because a greater number of children and adolescents who received once-daily doses had viral loads  $\geq 50$  copies/mL within 48 weeks.<sup>49</sup>

### *Dosing and Its Relation to Efficacy*

LPV/r is effective in treatment-experienced patients with severe immune suppression,<sup>50,51</sup> although heavily pretreated patients may be slower to reach undetectable viral loads<sup>51,52</sup> and may have less robust CD4 T lymphocyte cell (CD4) count percentage responses.<sup>53</sup>

The relationship between LPV exposure and the susceptibility of the HIV-1 isolate is a key component of successful treatment. The ratio of  $C_{\text{trough}}$  to half maximal effective concentration ( $EC_{50}$ ) is called the inhibitory quotient (IQ), and in both adults and children treated with LPV/r, viral load reduction is more closely associated with IQ than with either  $C_{\text{trough}}$  or  $EC_{50}$  alone.<sup>54-56</sup> One study investigated the use of the IQ as a guide for therapy by administering higher doses of LPV/r to children and adolescents until a target IQ of 15 was reached. This study showed that doses of LPV/r



400 mg/100 mg per m<sup>2</sup> of body surface area per dose twice daily (without FPV, NFV, NVP, or EFV) and LPV/r 480 mg/120 mg per m<sup>2</sup> of body surface area per dose twice daily (with NVP or EFV) were safe and tolerable.<sup>30</sup> Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and indicate the potential utility of TDM when LPV/r is used in children who were previously treated with PIs.<sup>57</sup> An LPV plasma concentration of  $\geq 1$  mcg/mL is cited as a minimum target C<sub>trough</sub>,<sup>58-60</sup> but this C<sub>trough</sub> may not adequately control viremia in patients with multiple LPV resistance mutations.<sup>61,62</sup>

## Formulations

### *Palatability*

The poor palatability of the LPV/r oral solution can be a significant challenge to medication adherence for some children and families. Numbing the taste buds with ice chips before or after administering the solution, masking the taste of the solution by administering it with sweet or tangy foods (e.g., chocolate syrup, peanut butter), or having the pharmacist flavor the solution prior to dispensing it are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.<sup>63-65</sup>

### *Do Not Use Crushed Tablets*

LPV/r tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed and result in significantly reduced AUC, maximum concentration (C<sub>max</sub>), and C<sub>trough</sub> compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets **cannot be recommended for use**.<sup>66</sup> In a PK study that used a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate LPV C<sub>trough</sub> measurements.<sup>48</sup>

## Toxicity

Children treated with LPV/r may have less robust weight gain and smaller increases in CD4 percentage than children treated with NNRTI-based regimens.<sup>32,67-71</sup> However, one study did not observe this difference in the effect of LPV/r on CD4 count,<sup>72</sup> and another study found that the difference did not persist after a year of therapy.<sup>35</sup> Some studies found no differences between the weight gain of children treated with LPV/r and those treated with EFV.<sup>70,73</sup> Switching to an EFV-based regimen at or after age 3 years removed the risk of LPV-associated metabolic toxicity, with no loss of virologic control (see Table 16 in [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#)).<sup>70,71</sup> Bone mineral density improved when children were treated with EFV-containing regimens instead of regimens that contained LPV/r.<sup>74</sup> Among 212 children randomized to either remain on an LPV/r-based regimen or switch to an EFV-containing regimen, osteocalcin—a biochemical marker of bone turnover—was higher in the LPV/r group than the EFV group at both 8 weeks and 2 years post-randomization. Levels of C-telopeptide of type 1 collagen and procollagen type I N-terminal propeptide did not differ between the two groups.<sup>75</sup> In a separate study, among 220 children with HIV (mean age 6.38 years), lower bone mass was observed in children on LPV/r-based regimens than those with EFV-based regimens over 2 years of follow-up.<sup>76</sup>

# Appendix A: Pediatric Antiretroviral Drug Information

## Entry and Fusion Inhibitors

Fostemsavir (FTR, Rukobia)

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

## Fostemsavir (FTR, Rukobia)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
Extended-release tablet: 600 mg	
For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a> .	
Dosing Recommendations	Selected Adverse Events
<p><b>Child and Adolescent (Aged &lt;18 Years) Dose</b></p> <ul style="list-style-type: none"> <li>The safety and efficacy of using fostemsavir (FTR) in children and adolescents aged &lt;18 years have not been established.</li> </ul> <p><b>Adult Dose</b></p> <ul style="list-style-type: none"> <li>One tablet twice daily</li> </ul>	<ul style="list-style-type: none"> <li>QT corrected (QTc) interval prolongation with higher than recommended dosages</li> <li>Increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>Can be taken with or without food</li> <li>Extended-release tablet must be swallowed whole. Do not chew, crush, or split tablets.</li> <li>Should not be coadministered with strong cytochrome P450 (CYP) 3A4 inducers of metabolism, such as rifampin, carbamazepine, phenytoin, and phenobarbital</li> <li>Potential for multiple drug interactions. Check concomitant medications before prescribing FTR.</li> <li>Tablets have a slight odor similar to vinegar.</li> </ul>
	Metabolism/Elimination
	<ul style="list-style-type: none"> <li>FTR tromethamine is a prodrug of temsavir (TMR), an HIV-1 glycoprotein 120 (gp-120)-directed attachment inhibitor.</li> <li>FTR is rapidly converted to TMR after oral administration. Metabolic pathways of TMR include hydrolysis (esterases) (36.1% of oral dose), oxidation (CYP3A4) (21.1% of oral dose), and uridine diphosphate glucotransferase (&lt;1% of oral dose).</li> <li>TMR is a substrate of CYP3A, esterases, P-glycoprotein, and breast cancer resistance protein (BCRP).</li> <li>TMR is an inhibitor of organic anion transporter (OAT) P1B1 and OATP1B3; TMR and two of its metabolites are inhibitors of BCRP.</li> </ul> <p><b>FTR Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required in patients with mild-to-severe hepatic impairment.</li> </ul> <p><b>FTR Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required in patients with renal impairment or those on hemodialysis.</li> </ul>

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Coadministration with strong cytochrome P450 3A inducers is contraindicated, because the plasma concentrations of the active metabolite, temsavir (TMR), are significantly reduced, which could result in loss of virologic efficacy.
- *Cardiac toxicity:* Caution is required when used in combination with drugs that are associated with prolongation of the **QT corrected for heart rate (QTc)** interval of the echocardiogram.
- *Oral contraceptives and gender-affirming hormonal therapy:* **TMR may increase ethinyl estradiol concentrations and risk of thrombosis. Do not exceed 30 mcg ethinyl estradiol daily when fostemsavir is co-administered with estrogen-based therapies. For gender-affirming hormonal therapy, estrogen concentrations can be monitored with dose adjustments as needed.**<sup>1</sup>
- *3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins):* TMR may increase plasma concentrations of statins, including rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and simvastatin. Use the lowest possible starting dose of statin, and monitor for statin-associated adverse effects.
- *Hepatitis C virus direct-acting antivirals:* TMR may increase plasma concentrations of grazoprevir and voxilaprevir due to organic anion transporting polypeptide (OATP) 1B1/3 inhibition.
- *Other antiretroviral (ARV) agents:* Drug interaction studies of fostemsavir (FTR) in combination with darunavir/cobicistat, darunavir/ritonavir, etravirine, and maraviroc have been conducted in healthy volunteers. FTR given in combination with these other ARVs was generally well tolerated, and no dose adjustments were required.<sup>2,3</sup>

## Major Toxicities

- *More common:* Nausea, fatigue, diarrhea (reported in  $\geq 5\%$  of patients)
- *Less common:* QTc prolongation with higher-than-recommended doses<sup>4</sup>; increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection

## Resistance

The International AIDS Society–USA maintains a list of [HIV drug resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

TMR showed reduced antiviral activity against HIV subtype AE (the predominant subtype found in Southeast Asia but not commonly found elsewhere in the world). Treatment-emergent glycoprotein 120 (gp120) genotypic substitutions at four key sites—S375, M434, M426, and M475—have been found in evaluable **participants** with virologic failure in clinical trials. However, overall frequency of polymorphisms previously associated with the potential to reduce susceptibility to TMR is low and should not be a barrier to its usage in patients with multidrug resistance.<sup>5</sup>

## Pediatric Use

FTR is an HIV-1 gp120-directed attachment inhibitor that is not approved for use in pediatric patients. FTR was approved by the U.S. Food and Drug Administration in 2020 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are experiencing virologic failure on their current regimen due to resistance, intolerance, or safety considerations.<sup>6</sup> A pharmacokinetic, safety, acceptability, and swallowability study of FTR in children and adolescents weighing  $\geq 20$  kg is open to enrollment (PENTA Foundation: NCT04648280). The dose selection of FTR for children and adolescents weighing  $\geq 20$  kg utilized a population pharmacokinetic model-based approach to achieve similar adult TMR exposures following FTR 600 mg twice daily dosing that was demonstrated to be safe and effective in the BRIGHT E study in heavily treatment-experienced patients.<sup>7</sup>

### *Efficacy in Clinical Trials*

The safety and efficacy of FTR in heavily treatment-experienced adults with HIV were evaluated in the BRIGHT E trial, a Phase 3, double-blind placebo-controlled trial. A total of 371 participants were enrolled into two cohorts (randomized and nonrandomized), depending on remaining treatment options. The randomized cohort included 272 participants, with at least one fully active drug in at least one but no more than two ARV classes that could be added to FTR. Participants received either FTR or a placebo twice daily for 8 days, in addition to their failing ARV regimen. On Day 8, participants treated with FTR had a significantly greater decrease in levels of HIV-RNA than those taking the placebo (0.79 vs. 0.17 log<sub>10</sub> copies, respectively).<sup>8</sup> After Day 8, all participants received FTR as part of an optimized regimen. In results reported through 48 weeks,<sup>8</sup> 54% of participants had an HIV viral load of  $<40$  copies/mL. At Week 96, 60% of participants<sup>6,9</sup> had HIV viral loads of  $<40$  copies/mL and a mean increase in CD4 T lymphocyte (CD4) cell counts of 205 cells/mm<sup>3</sup>. In 51% (27 out of 53) of evaluable participants with virologic failure, treatment-emergent gp120 genotypic substitutions were detected at four key sites—S375, M434, M426, and M475. In the randomized cohort, virologic response rates increased over time, between the 24-week and 96-week analyses. Response rates were associated with better susceptibility scores for new optimized treatment regimens.<sup>10</sup> Patients with the lowest CD4 counts at baseline were more likely to experience serious adverse events or death.<sup>10</sup>

An additional nonrandomized cohort of 99 patients who had no active drugs as treatment options but had FTR added to an optimized ARV regimen was studied. Of these, 38% achieved an HIV viral load of  $<40$  copies/mL at 48 weeks.<sup>8</sup> For this cohort, at 96 weeks,<sup>6</sup> 37% of participants had HIV viral loads of  $<40$  copies/mL, and the mean increase in CD4 counts was 119 cells/mm<sup>3</sup>.

Improvements in patient-reported outcomes in health-related quality of life were observed among participants in both cohorts of the BRIGHT E trial at 48 weeks.<sup>11</sup>

### *Mechanism of Action*

FTR tromethamine is a prodrug of TMR, an HIV-1 gp120-directed attachment inhibitor. FTR is rapidly converted to TMR after oral administration. TMR binds directly to the HIV-1 gp120 and prevents viral attachment and subsequent entry of virus into host T cells. FTR has a novel mechanism of action and no *in vitro* cross-resistance with other ARVs, and it can be used regardless of HIV-1 tropism.<sup>5</sup>

### *Pharmacokinetics*

FTR is pre-systemically metabolized to the active moiety TMR by alkaline phosphatase in the luminal surface of the small intestine, and then TMR is rapidly absorbed. In healthy adults, the estimated **half-life** is approximately 11 hours.<sup>12</sup>

## Ibalizumab (IBA, Trogarzo)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Single-Dose Vial for Intravenous Administration:</b> 200 mg/1.33 mL (150 mg/mL) in a single-dose vial. Each single-dose vial contains the following inactive ingredients: L-histidine, polysorbate 80, sodium chloride, and sucrose.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Child and Adolescent Dose</b></p> <ul style="list-style-type: none"> <li>The safety and efficacy of using ibalizumab (IBA) in children and adolescents has not been established.</li> </ul> <p><b>Adult Dose</b></p> <ul style="list-style-type: none"> <li>A single-loading dose infusion of IBA, 2,000 mg of diluted solution, is administered intravenously (IV) over 30 minutes.</li> <li>The maintenance dose of IBA is 800 mg given every 2 weeks. The maintenance dose can be given as 800 mg of diluted solution administered IV over 15 minutes or as 800 mg of undiluted solution given by IV push over 30 seconds.</li> <li>U.S. Food and Drug Administration approval of IBA is limited to heavily treatment-experienced adults with multidrug-resistant HIV infection who are experiencing treatment failure on their current regimen.</li> <li>IBA is used in combination with other antiretroviral drugs.</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea, dizziness, nausea, rash</li> <li>Immune reconstitution inflammatory syndrome</li> <li>In studies of cynomolgus macaque monkeys, IBA use during pregnancy was associated with reversible immunosuppression (CD4 T and B cell lymphopenia) in offspring with IBA exposure <i>in utero</i>. Whether this association exists for offspring of a human birthing parent treated with IBA during pregnancy is unknown.</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>For administration by IV infusion, the appropriate number of vials must be diluted in 250 mL of 0.9% sodium chloride injection.</li> <li>Using aseptic technique, withdraw 1.33 mL from each vial and transfer into a 250-mL bag of 0.9% sodium chloride for IV injection. Other IV diluents must not be used.</li> <li>Once diluted, the solution should be administered immediately. If not used immediately, the solution can be stored at room temperature for up to 4 hours or refrigerated for up to 24 hours. Refrigerated solution should be allowed to stand at room temperature for at least 30 minutes but no more than 4 hours prior to administration.</li> <li>Diluted solution is administered as an IV infusion, not as a bolus or IV push.</li> <li>Undiluted solution may be given by IV push over 30 seconds to administer the maintenance dose.</li> </ul>
	Metabolism/Elimination
	<ul style="list-style-type: none"> <li>Monoclonal antibodies are metabolized to peptides and amino acids.</li> </ul>

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Ibalizumab (IBA) is a humanized immunoglobulin G4 monoclonal antibody that blocks HIV entry into CD4 T lymphocyte (CD4) cells. Based on IBA's mechanism of action and target-



mediated drug disposition, drug–drug interactions are not expected. However, no drug interaction studies have been conducted.<sup>1</sup>

## Major Toxicities

- *More common:* Rash, diarrhea, headache, nausea, dizziness, depression<sup>1,2</sup>
- *Less common (more severe):* Immune reconstitution inflammatory syndrome, hypersensitivity reaction<sup>1</sup>

## Resistance

HIV has shown reduced susceptibility to IBA, as defined by a decrease in maximum percent inhibition, when HIV loses N-linked glycosylation sites in the V5 loop of glycoprotein 120.<sup>1-3</sup>

Phenotypic and genotypic test results showed no evidence of cross-resistance between IBA and any U.S. Food and Drug Administration (FDA)–approved classes of antiretroviral (ARV) drugs.<sup>4</sup> IBA exhibits ARV activity against R5-tropic, X4-tropic, and dual-tropic HIV.<sup>4</sup>

## Pediatric Use

### *Approval*

IBA is not approved by the FDA for use in pediatric patients. IBA was approved by the FDA in 2018 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are experiencing treatment failure on their current regimen.<sup>5</sup> IBA has an orphan drug designation exempting the requirement for pediatric studies under the Pediatric Research Equity Act. The FDA requested that the company (i.e., Theratechnologies) create a registry to collect prospective data in individuals exposed to IBA during pregnancy to monitor maternal and pregnancy outcomes, including adverse effects on the developing fetus, neonate, and infant. Health care providers are encouraged to report these adverse events to Theratechnologies by calling 1-833-23-THERA (1-833-23-4372).

### *Efficacy in Clinical Trials*

A TaiMed Biologics trial, TMB-301, was conducted in 40 adults aged 23 to 65 years who had body weights ranging from 50 kg to 130 kg, had resistance to ARV drugs from three classes, had been treated for at least 6 months on stable ARV regimens, had viral loads >1,000 copies/mL, and had viral sensitivity to at least one ARV drug.<sup>3,5</sup> Participants continued their current ARV regimens and received a 2,000-mg loading dose of IBA on Day 7 of the study. One week after the loading dose, participants optimized their ARV regimens. Participants received IBA 800 mg on Day 21 and every 2 weeks thereafter. At Week 25, 43% of participants achieved suppressed viral loads<sup>1,3</sup> of <50 copies/mL. At Week 48 of an open-label extension study, 24 participants were taking IBA and their optimized ARV regimen. Sixteen of 27 participants (59%) had viral loads <50 copies/mL at 48 weeks.<sup>6,7</sup>

## ***Mechanism of Action***

IBA is a recombinant humanized monoclonal antibody that blocks HIV from infecting CD4 cells. It does this by binding to domain 2 of the CD4 receptor, which interferes with the post-attachment steps that allow HIV virus particles to enter host cells and prevent the viral transmission that occurs via cell–cell fusion.<sup>1,7</sup> IBA does not interfere with CD4-mediated immune functions because it binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor, away from major histocompatibility complex II molecule binding sites.

## ***Embryo-Fetal Toxicity***

In an enhanced prenatal and postnatal development study, pregnant cynomolgus monkeys were administered intravenous doses of IBA, and significant changes in infant monkey immune cell levels were found (CD4 T cell and B cell lymphocytopenia) that were attributed to *in utero* IBA exposure.<sup>1</sup> The lymphocyte changes correlated with infant monkey IBA serum concentrations and appeared to return to near-normal levels when IBA concentrations were nearly undetectable. One treatment-group infant monkey died from a systemic viral infection with secondary superficial bacterial infection that was acquired during the postnatal period. Despite the low incidence of death (1 of 20 infant monkeys), the death may be related to IBA-induced immunosuppression.<sup>1</sup>

Based on these animal data, IBA may cause reversible immunosuppression (CD4 T cell and B cell lymphocytopenia) in infants born to **human birthing parents** who were treated with IBA during pregnancy. Immune phenotyping of the peripheral blood and expert consultation are recommended to provide guidance regarding monitoring and management of exposed infants based on the degree of immunosuppression observed. Furthermore, the safety of administering live or live-attenuated vaccines to infants with *in utero* IBA exposure and abnormal lymphocyte levels is unknown.

## Maraviroc (MVC, Selzentry)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations																																							
<p>Oral Solution: 20 mg/mL</p> <p>Tablets: 25 mg, 75 mg, 150 mg, 300 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>																																							
Dosing Recommendations		Selected Adverse Events																																					
<ul style="list-style-type: none"> <li>Maraviroc (MVC) is approved by the U.S. Food and Drug Administration (FDA) for use, in combination with other antiretroviral (ARV) agents, for the treatment of CCR5-tropic HIV-1 infection in infants born full term and weighing <math>\geq 2</math> kg, children, adolescents, and adults.</li> </ul> <p><b>Recommended MVC Dose for Full-Term Infants and Treatment-Experienced Children and Adolescents Weighing <math>\geq 2</math> kg: Tablets or Oral Solution</b></p> <table border="1"> <thead> <tr> <th>Weight Band</th> <th>Twice-Daily Dosing</th> <th>Oral Solution (20 mg/mL)</th> <th>Tablets</th> </tr> </thead> <tbody> <tr> <td colspan="4">Recommended doses when MVC is given with noninteracting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (T-20), and raltegravir (RAL)</td> </tr> <tr> <td>2 kg to &lt;4 kg</td> <td>30 mg</td> <td>1.5 mL</td> <td>N/A</td> </tr> <tr> <td>4 kg to &lt;6 kg</td> <td>40 mg</td> <td>2 mL</td> <td>N/A</td> </tr> <tr> <td>6 kg to &lt;10 kg</td> <td>100 mg</td> <td>5 mL</td> <td>One 25-mg tablet and one 75-mg tablet</td> </tr> <tr> <td>10 kg to 14 kg</td> <td>150 mg</td> <td>7.5 mL</td> <td>One 150-mg tablet</td> </tr> <tr> <td>14 kg to &lt;30 kg</td> <td>200 mg</td> <td>10 mL</td> <td>One 150-mg tablet and two 25-mg tablets</td> </tr> <tr> <td>30 kg to &lt;40 kg</td> <td>300 mg</td> <td>15 mL</td> <td>One 300-mg tablet</td> </tr> <tr> <td><math>\geq 40</math> kg</td> <td>300 mg</td> <td>15 mL</td> <td>One 300-mg tablet</td> </tr> </tbody> </table>		Weight Band	Twice-Daily Dosing	Oral Solution (20 mg/mL)	Tablets	Recommended doses when MVC is given with noninteracting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (T-20), and raltegravir (RAL)				2 kg to <4 kg	30 mg	1.5 mL	N/A	4 kg to <6 kg	40 mg	2 mL	N/A	6 kg to <10 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet	10 kg to 14 kg	150 mg	7.5 mL	One 150-mg tablet	14 kg to <30 kg	200 mg	10 mL	One 150-mg tablet and two 25-mg tablets	30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet	$\geq 40$ kg	300 mg	15 mL	One 300-mg tablet	<ul style="list-style-type: none"> <li>Nausea, vomiting</li> <li>Abdominal pain, diarrhea</li> <li>Cough</li> <li>Upper respiratory tract infections</li> <li>Fever</li> <li>Rash</li> <li>Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)</li> <li>Postural hypotension (generally seen in patients with severe renal insufficiency)</li> <li>Dizziness</li> </ul>	
Weight Band	Twice-Daily Dosing	Oral Solution (20 mg/mL)	Tablets																																				
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		Special Instructions																																					
		<ul style="list-style-type: none"> <li>MVC is recommended for use in patients who have only CCR5-tropic HIV-1. Before using MVC, conduct testing with an HIV tropism assay (see <a href="#">Drug-Resistance Testing</a> in the <a href="#">Adult and Adolescent Antiretroviral Guidelines</a>) to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use MVC if CXCR4-tropic or mixed/dual-tropic HIV is present.</li> <li>MVC can be given without regard to food.</li> <li>Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.</li> <li>Use caution when administering MVC to patients with underlying cardiac disease.</li> </ul>																																					

Recommended doses when MVC is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs)				<h3 style="text-align: center;">Metabolism/Elimination</h3> <ul style="list-style-type: none"> <li>MVC is a substrate of CYP3A4. If a patient is receiving ARV agents or other medications that act as CYP3A inducers or inhibitors, the dose of MVC should be adjusted accordingly.</li> </ul> <p><b>MVC Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>Use caution when administering MVC to patients with hepatic impairment; MVC concentrations may be increased in these patients.</li> </ul> <p><b>MVC Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>No data recommend specific doses of MVC for pediatric patients with mild or moderate renal impairment. MVC is <b>contraindicated</b> for pediatric patients with severe renal impairment or end-stage renal disease who are on regular hemodialysis and who are receiving potent CYP3A inhibitors.</li> <li>Refer to the manufacturer's prescribing information for the appropriate doses to use in adolescent and adult patients with renal impairment.</li> </ul>
2 kg to <10 kg	<b>Not recommended.</b> Data are insufficient to make dosing recommendations for infants weighing <10 kg and receiving a potent P450 CYP3A inhibitor.			
10 kg to <20 kg	50 mg	2.5 mL	Two 25-mg tablets	
20 kg to <30 kg	75 mg	4 mL	One 75-mg tablet	
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet	
≥40 kg	150 mg	7.5 mL	One 150-mg tablet	
Recommended doses when MVC is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz (EFV) and etravirine (ETR)				
Infants and children and adolescents in all weight bands	<b>Not recommended.</b> Data are insufficient to make dosing recommendations.			
<b>Recommended MVC Dose for Adults: Tablets</b>				
<b>When Coadministered with</b>		<b>Dose</b>		
Noninteracting concomitant medications, including NRTIs, T-20, NVP, and RAL		300 mg twice daily		
Potent CYP3A inhibitors (with or without a potent CYP3A inducer), including all PIs		150 mg twice daily		
Potent CYP3A inducers (without a potent CYP3A inhibitor), including EFV and ETR		600 mg twice daily		

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Absorption:** Absorption of maraviroc (MVC) is slightly reduced with ingestion of a high-fat meal. Food restrictions were not part of either the adult trials (which used the tablet formulation) or the pediatric trial (which used both the tablet and oral solution formulations) that demonstrated the efficacy, antiviral activity, and safety of MVC. Therefore, MVC can be given with or without food.

- *Metabolism:* MVC is a cytochrome P450 (CYP) 3A and p-glycoprotein (P-gp) substrate and requires dose adjustments when administered with medications that modulate CYP3A or P-gp. A patient's medication profile should be carefully reviewed for potential drug interactions before MVC is administered; recommended MVC doses are based on concomitant medications and their anticipated effect on MVC metabolism.

## Major Toxicities

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, vomiting, diarrhea, and headache. Dizziness occurred in 12.2% of adults but only 3.2% of children when MVC was administered twice daily.
- *Less common (more severe):* Hepatotoxicity has been reported; some cases were preceded by evidence of a systemic allergic reaction (including pruritic rash, eosinophilia, or elevated levels of immunoglobulin). Serious adverse events (AEs) occurred in <2% of MVC-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

## Mechanism of Action

MVC is a CCR5 receptor antagonist that selectively binds to the human chemokine receptor CCR5 on the cell membrane, preventing interaction between HIV-1 glycoprotein 120 and CCR5 tropic HIV-1, inhibiting viral entry into the cell.

## Resistance

An HIV tropism assay should be performed before MVC is administered to a patient. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants. However, in circumstances when MVC is needed for presumptive HIV therapy for full-term neonates at high risk of perinatal HIV transmission, initiation of MVC should not be deferred until assay results are available, and consultation with an HIV expert is recommended.

## Pediatric Use

### *Approval*

MVC is approved by the U.S. Food and Drug Administration (FDA) for treatment of CCR5-tropic HIV virus, when used in conjunction with other antiretroviral drugs, in full-term infants weighing  $\geq 2$  kg, children, adolescents, and adults.<sup>1,2</sup>

### *Pharmacokinetics and Efficacy*

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2007) study evaluated the pharmacokinetics (PK) and safety of MVC added to a 6-week prophylactic antiretroviral regimen to prevent perinatal HIV transmission of HIV among infants born to mothers with HIV.<sup>2</sup> Analyses were stratified by exposure to efavirenz (EFV), either *in utero* or through breastmilk, versus non-EFV exposure. The MVC exposure target was average plasma concentration ( $C_{avg}$ )  $\geq 75$  ng/mL, as determined by adult treatment studies. MVC oral solution was

dosed at 8 mg/kg twice daily for the first 6 weeks of life. Among 25 infants with evaluable PK data, 12 of whom were EFV-exposed, 67% of the EFV-exposed infants achieved a  $C_{avg} \geq 75$  ng/mL at Week 1, whereas 77% of the EFV-unexposed infants had a  $C_{avg} \geq 75$  ng/mL. At Week 4, the proportion of infants achieving a  $C_{avg} \geq 75$  ng/mL declined to 42% among EFV-exposed infants and 31% among EFV-unexposed infants. No infants in the study met safety endpoints or discontinued MVC during the study, and no infants acquired HIV. The FDA recommendation for MVC dosing among children >6 weeks of life but younger than 2 years of age is based on modeling using PK data from the IMPAACT 2007 study. A population PK model, which included assessment of age and maturational changes, was developed from IMPAACT 2007 data to describe MVC disposition within the first 6 weeks of life.<sup>3</sup> Simulations with FDA-approved weight-band dosing resulted in the majority of simulated patients (84.3%) achieving an average concentration of  $\geq 75$  ng/mL. When considering the use of MVC for neonates and infants, a pediatric HIV specialist should be consulted.

PK, safety, and efficacy of MVC for treatment-experienced children ages 2 years to <18 years and weighing  $\geq 10$  kg, and who had plasma HIV RNA >1,000 copies/mL were examined in an international dose-finding and efficacy study (A4001031). Of the 103 children who participated in the study, 51% had HIV-1 subtype C, 25% had subtype B, and 23% had other subtypes.

In this trial, the MVC dose was based on body surface area and the composition of the patient's optimized background therapy. Most participants (90 of 103 participants [87%]) received MVC in combination with potent CYP3A inhibitors; 10 participants received MVC with noninteracting medications; and only 3 participants received MVC with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean  $C_{avg} > 100$  ng/mL) was achieved with both the tablet and oral solution formulation of MVC.<sup>4</sup>

From a mean baseline plasma HIV RNA concentration of 4.4  $\log_{10}$  copies/mL, a decrease of  $\geq 1.5 \log_{10}$  occurred in all four age-based cohorts. Only two participants discontinued the study due to AEs. The most common MVC-related AEs through 48 weeks were diarrhea (which occurred in 20.3% of participants), vomiting (19.8%), and upper respiratory infections (16.2%). At Week 48, 48% of participants had HIV RNA <48 copies/mL.<sup>4</sup> The absolute CD4 T lymphocyte cell count and percentage increased in all four subgroups of the study, with overall median increases of 192 cells/mm<sup>3</sup> (interquartile range [IQR] 92–352 cells/mm<sup>3</sup>) and 4% (IQR 1% to 8%), respectively.

# Appendix A: Pediatric Antiretroviral Drug Information

## Integrase Inhibitors

Bictegravir (BIC)

Cabotegravir (CAB, Vocabria)

Dolutegravir (DTG, Tivicay)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)



# Bictegravir (BIC)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations							
<p>Bictegravir is available only in a fixed-dose combination (FDC) tablet.</p> <p><b>FDC Tablet</b></p> <ul style="list-style-type: none"> <li>[Biktarvy]               <ul style="list-style-type: none"> <li>Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg</li> <li>Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg</li> </ul> </li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>							
Dosing Recommendations	Selected Adverse Events						
<p><b>[Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)</b></p> <p><i>Neonate or Child Aged &lt;2 Years and Weighing &lt;14 kg</i></p> <ul style="list-style-type: none"> <li>No data currently are available on the appropriate dose of Biktarvy in children aged &lt;2 years and weighing &lt;14 kg. Studies are being conducted to develop an age-appropriate formulation and identify the appropriate dose for this age and weight group.</li> </ul> <p><i>Child (Aged ≥2 Years), Adolescent, and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with or without food</li> </ul> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #d9e1f2;">Body Weight</th> <th style="background-color: #d9e1f2;">Dose</th> </tr> </thead> <tbody> <tr> <td>≥14 to &lt;25 kg</td> <td>BIC 30 mg/FTC 120 mg/TAF 15 mg</td> </tr> <tr> <td>≥25 kg</td> <td>BIC 50 mg/FTC 200 mg/TAF 25 mg</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>The U.S. Food and Drug Administration approved Biktarvy for use in only antiretroviral therapy-naïve patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA &lt;50 copies/mL) on a stable ARV regimen and who have no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy. Some members on the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation but no other known mutations associated with resistance to the individual components of Biktarvy (see the Efficacy in Clinical Trials in Adults section below).</li> </ul>	Body Weight	Dose	≥14 to <25 kg	BIC 30 mg/FTC 120 mg/TAF 15 mg	≥25 kg	BIC 50 mg/FTC 200 mg/TAF 25 mg	<ul style="list-style-type: none"> <li>Diarrhea, nausea, headache</li> </ul>
Body Weight	Dose						
≥14 to <25 kg	BIC 30 mg/FTC 120 mg/TAF 15 mg						
≥25 kg	BIC 50 mg/FTC 200 mg/TAF 25 mg						
	Special Instructions						
	<ul style="list-style-type: none"> <li>Administer Biktarvy with or without food. See the Drug Interactions section below for guidance when administering Biktarvy with antacids or iron or calcium supplements.</li> <li>For children who are unable to swallow a whole tablet, the tablet can be split and each part taken separately, as long as all parts are swallowed within approximately 10 minutes. Dissolving tablets may be an alternative, but crushing tablets is <b>not recommended</b>.</li> <li>Screen patients for hepatitis B virus (HBV) infection before using FTC or TAF. Severe acute exacerbation of HBV can occur when discontinuing FTC or TAF; therefore, monitor hepatic function for several months after halting therapy with FTC or TAF.</li> </ul>						
	Metabolism/Elimination						
	<ul style="list-style-type: none"> <li>BIC is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.</li> </ul>						

	<p><b>Biktarvy Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>• Biktarvy is <b>not recommended</b> for use in patients with severe hepatic impairment.</li> </ul> <p><b>Biktarvy Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• Biktarvy is <b>not recommended</b> for use in <b>pediatric</b> patients with estimated creatinine clearance &lt;30 mL/min. See the <a href="#">Biktarvy product label</a> for use in <b>adult</b> patients on dialysis.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- **Metabolism:** Bictgravir (BIC) is a substrate of cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. Tenofovir alafenamide (TAF) is a substrate of P-glycoprotein and UGT1A1. Coadministration of the fixed-dose combination (FDC) tablet bictgravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF [Biktarvy]) and rifampin is **contraindicated**.<sup>1,2</sup>
- **Renal effects:** BIC is an inhibitor of organic cation transporter 2 and multidrug and toxin extrusion protein 1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate (eGFR) with no change in glomerular function. Drugs that decrease renal function could reduce clearance of emtricitabine (FTC).
- **Absorption:** Administering BIC concurrently with antacids lowers the plasma concentrations of BIC. This phenomenon occurs because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Chelation by high concentrations of divalent cations, such as iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and BIC. For this reason, Biktarvy should be administered at least 2 hours before or 6 hours after antacids and supplements or multivitamins that contain iron, calcium, aluminum, magnesium, and/or zinc<sup>3</sup> when Biktarvy is given on an empty stomach. Biktarvy and antacids or supplements that contain calcium or iron can be taken together with food.

## Major Toxicities

- **More common:** Diarrhea, nausea, headache. In two clinical trials, total bilirubin increased by up to 2.5 times the upper limit of normal in 12% of patients who received Biktarvy. In general, however, bilirubin increase was mild and did not lead to drug discontinuations in these trials.<sup>2</sup> BIC may cause an increase in creatine kinase concentration. One patient out of 201 in a postmarketing observational study in adults experienced thrombocytopenia,<sup>4</sup> and 1 participant out of 100 in a prospective cohort study in children and adolescents experienced insomnia/anxiety<sup>5</sup> leading to drug discontinuation. Other neuropsychiatric and central nervous system manifestations have been reported in adults (see [Table 17a. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity](#)). Weight gain has been reported in adults who were receiving Biktarvy,<sup>6,7</sup> with an associated **increased risk of cardiometabolic complications,<sup>8</sup> but preliminary pediatric data regarding weight**

gain appear to be inconsistent<sup>9,10</sup> (see [Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain](#)).

- *Less common (more severe)*: Severe immune reconstitution inflammatory syndrome may be more common with INSTIs than with other antiretroviral (ARV) agents. Drug reaction with eosinophilia and systemic symptoms, or DRESS, syndrome has been reported in an adult starting a BIC-containing regimen.<sup>11</sup> Additionally, two cases of drug-induced liver injury—one leading to death—have been reported in adult women with HIV who were switched to a BIC-containing regimen.<sup>12,13</sup>

## Resistance

The International Antiviral Society–USA maintains a list of [HIV drug resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

BIC—available as part of the FDC tablet Biktarvy, which contains BIC 50 mg/FTC 200 mg/TAF 25 mg—was approved by the U.S. Food and Drug Administration (FDA) in 2018 for use in adults and in 2019 for use in children or adolescents weighing  $\geq 25$  kg. Biktarvy, containing BIC 30 mg/FTC 120 mg/TAF 15 mg, was approved by the FDA in 2021 for use in children aged  $\geq 2$  years and weighing  $\geq 14$  to  $< 25$  kg. Biktarvy is FDA-approved for patients who have no ARV treatment history or to replace current ARV regimens in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known mutations associated with resistance to the individual components of the FDC.<sup>2</sup> However, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation but no other known mutations associated with resistance to the individual components of Biktarvy (see the Efficacy in Clinical Trials in Adults section below).

### *Clinical Efficacy in Adults*

In a short-term Phase 1 study, BIC monotherapy at doses of BIC 50 mg or BIC 100 mg was well tolerated. Three out of eight participants in both of these dosing groups achieved HIV RNA  $< 50$  copies/mL within 11 days.<sup>14</sup> The efficacy (defined as viral load suppression to HIV RNA  $< 50$  copies/mL) and safety (as measured by the incidence of study drug discontinuation or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naïve adults. Viral load suppression occurred in 89% of participants who received coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg ( $n = 320$ ) and in 93% of participants who received a regimen of dolutegravir (DTG) 50 mg plus FTC 200 mg plus TAF 25 mg ( $n = 325$ ). Study drug discontinuation occurred in 1% of participants in both groups.

In a separate trial, viral load suppression occurred in 92% of participants who received BIC/FTC/TAF ( $n = 314$ ) and in 93% of participants who received coformulated abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) ( $n = 315$ ). Study drug discontinuation was not reported for any of the participants who received BIC/FTC/TAF, although it

did occur in 1% of participants who received ABC/DTG/3TC.<sup>2,15</sup> Studies that randomized virologically suppressed patients who were on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. Viral load suppression occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (n = 282) and in 95% of participants who continued taking ABC/DTG/3TC (n = 281). Study drug discontinuation was reported in 2% of participants who received BIC/FTC/TAF and 1% of participants who received ABC/DTG/3TC. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (n = 290) achieved viral load suppression, whereas 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (n = 287) achieved viral load suppression. Study drug discontinuation occurred in 1% of participants in both groups.<sup>2</sup> In an open-label extension following two randomized trials, 98.6% (426 of 432) (95% confidence interval [CI], 97.0% to 99.5%) of participants with available viral load data at week 240 maintained HIV RNA <50 copies/mL; in an analysis counting missing viral loads as failures, 67.2% (426 of 634) (95% CI, 63.4% to 70.8%) met viral suppression criteria. No treatment-emergent resistance to BIC/FTC/TAF was detected, and adverse events led to drug discontinuation in 1.6% of participants.<sup>6</sup> Similar BIC/FTC/TAF efficacy has been demonstrated in historically underrepresented populations, including Black and female populations with HIV.<sup>16,17</sup>

Initial studies in participants switching to BIC/FTC/TAF from stable antiretroviral therapy (ART) required undetectable viral load for 3 or 6 months and no proven or presumed preexisting resistance to any of the components of BIC/FTC/TAF.<sup>2,18,19</sup> Further analysis of data from these studies used proviral genotyping and showed presence of M184V/I mutation in 54 (10%) of 543 BIC/FTC/TAF-treated participants. Presence of this mutation did not affect viral load suppression, with Week 48 HIV RNA <50 copies/mL in 52 (96%) of 54 participants with archived M184V/I mutations compared with Week 48 HIV RNA <50 copies/mL in 561 (98%) of 570 participants without the mutation.<sup>20</sup> A study to measure the effect of preexisting nucleoside reverse transcriptase inhibitor (NRTI) mutations on virologic outcome in participants switching from a stable regimen to BIC/FTC/TAF showed Week 48 HIV RNA <50 copies/mL in 223 (94%) of 237 participants without M184V/I resistance and in 42 (89%) of 47 participants with M184V/I mutations at baseline.<sup>21,22</sup> At Week 48, HIV RNA <50 copies/mL was maintained in 199 (93%) of 213 participants with no NRTI resistance mutation and in 66 (93%) of 71 participants with any NRTI resistance mutation, including K65R/E/N, any number of thymidine analogue mutations (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N), T69 insertions, T69D, K70E/G/M/Q/S/T, L74I/V, V75A/S/M/T, Y115F, Q151M, or M184V/I.<sup>21</sup> That study required pre-enrollment virologic suppression for 6 months in those with suspected NRTI resistance and 3 months for those without suspected NRTI resistance.<sup>21</sup> In an analysis of participant data pooled from six clinical trials switching virologically suppressed adults with HIV to BIC/FTC/TAF, 98% (179 of 182) of participants with pre-existing M184V/I and 99% (2,012 of 2,034) of all participants (with or without M184V/I) had an HIV-1 RNA viral load <50 copies/mL at their last on-treatment visit, with no treatment-emergent resistance to BIC/FTC/TAF.<sup>21,23-25</sup> In a retrospective review at a single center in Spain involving 506 treatment-experienced adults with HIV who started BIC/FTC/TAF with a viral load <50 copies/mL, 69 (13.6%) had documented preexisting NRTI resistance mutations (11.2% M184V/I and 5.9% tenofovir mutations). In the intention-to-treat analysis, the proportion with a viral load <50 copies/mL was 88.4% (61/69) in those with NRTI resistance mutations versus 82.2% (359 of 437) in those without NRTI resistance mutations. In the per-protocol analysis, the proportions were 93.8% (61 of 65) in those with NRTI resistance mutations versus 94.4% (359 of 380) in those without NRTI mutations.<sup>26</sup> In another analysis from an HIV program in Canada using electronic health records from 50 adults with major NRTI resistance mutations prior to starting BIC/FTC/TAF, 49 had a viral load

<100 copies/mL at a mean of 18.6 months after starting the regimen, with the remaining patient having questionable adherence.<sup>27</sup> In practice, Panel members have used BIC/FTC/TAF even in patients with detectable viral load, prior ARV failure, or virus containing the M184V mutation but no other known mutations associated with resistance to the individual components of Biktarvy. This practice is based on the premise that the ability to simplify multi-pill or multi-dose regimens to a single small pill, once daily, can overcome potential resistance barriers with definite adherence benefits.<sup>28</sup>

## Pharmacokinetics

Pharmacokinetic (PK) studies of Biktarvy containing BIC 50 mg have been performed in adults, adolescents aged 12 years to <18 years who weigh  $\geq 35$  kg, and children aged 6 years to <12 years who weigh  $\geq 25$  kg. PK studies of “low-dose” Biktarvy, which contains BIC 30 mg, have been performed in children aged  $\geq 2$  years weighing 14 to <25 kg.<sup>29</sup> These studies show a higher BIC maximum serum concentration ( $C_{max}$ ) in the younger cohorts than in the older cohorts, perhaps because the administered dose is higher on a mg/kg basis (see [Table A](#) below). The lower trough serum concentration ( $C_{tau}$ ) and higher  $C_{max}$  in the younger age/lower body weight cohorts suggest more rapid clearance in children and adolescents than in adults. In the cohorts with body weight<sup>29</sup>  $\geq 14$  to <25 kg and body weight<sup>5</sup>  $\geq 35$  kg, there is a lower geometric mean ratio when  $C_{tau}$  is compared to adult values, and the lower 90% CI suggests that some patients have quite rapid clearance (see [Table B](#) below). These PK observations raise the concern that some of the patients in the youngest age/lowest body weight cohorts may experience suboptimal trough concentrations, which may lead to less “pharmacologic forgiveness” in people with lower adherence (see [Table B](#) below).<sup>30</sup>

**Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV**

PK Parameters	Children Aged $\geq 2$ Years and Weighing $\geq 14$ to <25 kg	Children Aged 6 Years to <12 Years and Weighing $\geq 25$ kg	Adolescents Aged 12 Years to <18 Years and Weighing $\geq 35$ kg	Adults
Dose (mg)	30	50	50	50
Dose for Lowest Weight in the Cohort (mg/kg)	2.14	2	1.43	1.25 <sup>a</sup>
AUC <sub>tau</sub> ng•h/mL Mean (CV%)	109,000 (24)	128,000 (28)	89,100 (31)	102,000 (26.9)
C <sub>max</sub> ng/mL Mean (CV%)	10,100 (21)	9,460 (24)	6,240 (27)	6,150 (22.9)
C <sub>tau</sub> ng/mL Mean (CV%)	2,000 (78)	2,360 (39)	1,780 (44)	2,610 (35.2)

<sup>a</sup> This dose was calculated using 40 kg as the lowest weight for adults.

**Key:** AUC<sub>tau</sub> = area under the concentration time curve over the dosing interval; C<sub>max</sub> = maximum serum concentration; C<sub>tau</sub> = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

**Sources:** Majeed S, German P, West SK, et al. B/F/TAF low-dose tablet relative bioavailability in HVs and PK in children with HIV. Abstract #841. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, MA. Available at: [https://www.natap.org/2020/CROI/croi\\_111.htm](https://www.natap.org/2020/CROI/croi_111.htm)

Gaur AH, Cotton MF, Rodriguez CA, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, Phase 2/3 trial. *Lancet Child Adolesc Health*. 2021;5(9):642-651. Available at: <https://pubmed.ncbi.nlm.nih.gov/34302760>.



**Table B. Bictegravir Pharmacokinetics in Children and Adolescents with HIV**

Cohort Characteristics	Dose (mg)	Dose for Lowest Weight in Cohort (mg/kg)	GMR% (90% CI) Compared to Adult Values <sup>a</sup>		
			AUC <sub>tau</sub>	C <sub>max</sub>	C <sub>tau</sub>
<b>Aged ≥2 Years and Weighing ≥14 to &lt;25 kg<sup>29</sup></b>	30	2.14	109 (96.7–122)	166 (149–184)	67.7 (49.6–92.4)
<b>Aged 6 Years to &lt;12 Years and Weighing ≥25 kg<sup>5</sup></b>	50	2	125 (117–134)	153 (143–163)	88.9 (80.6–98.0)
<b>Aged 12 Years to &lt;18 Years and Weighing ≥35 kg<sup>5</sup></b>	50	1.43	86 (80–93)	100 (94–107)	65.4 (58.3–73.3)

<sup>a</sup> In this table, child and adolescent pharmacokinetic (PK) values are compared with the PK values of adults who received bictegravir 50 mg. The dose for the lowest weight in the adult cohort was 1.25 mg/kg; this was calculated using 40 kg as the lowest weight for adults.

Key: AUC<sub>tau</sub> = area under the concentration time curve over the dosing interval; C<sub>max</sub> = maximum serum concentration; C<sub>tau</sub> = trough serum concentration at the end of the dosing interval; CI = confidence interval; GMR = geometric mean ratio

### ***Use of Biktarvy in Children and Adolescents Weighing ≥25 kg***

BIC 50 mg/FTC 200 mg/TAF 25 mg (Biktarvy) was administered to adolescents aged 12 years to <18 years who weighed ≥35 kg (maximum body weight 56.1 kg) and who had maintained viral loads of <50 copies/mL for ≥6 months on their previous ARV regimens. The drug was well tolerated and was associated with a fall in eGFR similar to that seen in adults. This decrease in eGFR was considered to be from changes in tubular secretion of creatinine and was not a true change in glomerular function. In comparing cohorts of children (body weight ≥14 to <25 kg) and adolescents (body weight ≥35 kg) with adult cohorts, the geometric mean ratio of C<sub>tau</sub> was noted to be lower (see Tables A and B above). All 50 participants in the study had viral loads <50 copies/mL at Week 24, and 49 of 50 had viral loads <50 copies/mL at week 48.<sup>5</sup>

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.<sup>5</sup> Despite a high area under the curve (AUC) and C<sub>max</sub> (see [Table A](#) above), the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies. One participant stopped the study drug because of insomnia and anxiety. The geometric mean ratio of C<sub>tau</sub> compared with adult values (see [Table B](#) above) showed trough concentrations similar to those seen in adults.<sup>5</sup> All 50 participants in the study had viral loads <50 copies/mL at Week 24, and 49 of 50 had viral loads <50 copies/mL at Week 48.<sup>5</sup>

### ***Use of Biktarvy in Children Weighing ≥14 to <25 kg***

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF15 mg were administered to children aged ≥2 years weighing ≥14 to <25 kg and who had viral loads <50 copies/mL on stable ART. PK evaluation showed high AUC and C<sub>max</sub>, similar to those in patients aged 6 years to <12 years who weighed ≥25 kg, a similarly low C<sub>tau</sub> (see [Table A](#) above), and a lower geometric mean ratio when C<sub>tau</sub> was compared with adult values (see [Table B](#) above).<sup>29</sup> In general, the low-dose tablet was well tolerated over 55 weeks in the 22 children studied.<sup>31</sup> Adverse events considered related to the study

drug included transient neutropenia (n = 2) and abdominal pain (n = 3).<sup>31</sup> At 24 weeks, the median change in CD4 cell count was a decrease of 100 cells/ $\mu$ L, and the change in CD4 percentage was an increase of 0.5%. HIV RNA at <50 copies/mL was maintained in 20 of 22 participants at 24 weeks.<sup>31</sup>

### ***Dosing: Splitting, Dissolving, or Crushing Biktarvy Tablets***

The product label states that for children who are unable to swallow a whole tablet, the tablet can be split and each part taken separately, as long as all parts are ingested within approximately 10 minutes.<sup>2</sup> Dissolving BIC/FTC/TAF tablets may be an alternative method of administration, but crushing tablets **is not recommended**.

In a Phase 1 open-label, single-dose, three-period crossover randomized trial of 18 adult participants without HIV, the bioavailability of Biktarvy (BIC 50 mg/FTC 200 mg/TAF 25 mg) was evaluated in fasting participants who received Biktarvy dissolved in water, crushed in applesauce, or as a solid tablet. Dissolved tablet plasma concentration AUC was considered bioequivalent for all ARV components. Although the dissolved tablet  $C_{max}$  was considered bioequivalent for BIC and FTC, the TAF  $C_{max}$  90% lower confidence limit was not (dissolved vs. solid ratio, 96% [90% CI, 74% to 124%]). For crushed tablets mixed with applesauce, the BIC component was considered bioequivalent for AUC and  $C_{max}$ . However, crushed FTC and TAF AUC and  $C_{max}$  were lower than that of solid tablets, with FTC  $C_{max}$  (crushed vs. solid ratio, 70% [90% CI, 63% to 78%]), TAF AUC (84% [90% CI, 69% to 103%]), and TAF  $C_{max}$  (66% [90% CI, 51% to 85%]) failing to meet bioequivalence criteria. Crushing Biktarvy tablets may lead to suboptimal FTC and TAF exposures.<sup>32</sup>

In the clinical literature, case reports in adults with HIV receiving crushed BIC/FTC/TAF describe inconsistent virological and resistance outcomes.<sup>24,33-36</sup> These cases varied in underlying comorbidities, baseline viral loads, adherence, method of crushing and dissolving tablets, administration (i.e., orally vs. via a tube), and instructions about polyvalent cation and food administration.



# Cabotegravir

Updated: June 27, 2024

Reviewed: June 27, 2024

Cabotegravir (CAB, Vocabria)

Cabotegravir for Intramuscular Injection (CAB, Apretude)

Cabotegravir and Rilpivirine for Intramuscular Injections (Long-Acting Injectable CAB and RPV, Cabenuva)

Formulations	
<p><b>Tablet</b></p> <ul style="list-style-type: none"> <li>[Vocabria] Cabotegravir: 30 mg</li> </ul> <p><b>Single-Dose Vial for Intramuscular Injection</b></p> <ul style="list-style-type: none"> <li>[Apretude] Cabotegravir 600-mg/3-mL (200-mg/mL) suspension for intramuscular injection for use as HIV pre-exposure prophylaxis only</li> </ul> <p><b>Co-packaged Formulations</b></p> <ul style="list-style-type: none"> <li>[Cabenuva Kit] Cabotegravir 400-mg/2-mL (200-mg/mL) and rilpivirine 600-mg/2-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe)</li> <li>[Cabenuva Kit] Cabotegravir 600-mg/3-mL (200-mg/mL) and rilpivirine 900-mg/3-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe)</li> </ul> <p>When using the co-packaged formulation, refer to the <a href="#">Rilpivirine</a> section for additional information.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>[Apretude] Cabotegravir (CAB) for Intramuscular Injection</b></p> <ul style="list-style-type: none"> <li>CAB 600 mg/3 mL for intramuscular (IM) injection is approved by the U.S. Food and Drug Administration (FDA) for use as HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing <math>\geq 35</math> kg; an oral dosing lead-in period of approximately 1 month is optional. See package insert for additional information about dosing and administration of CAB as PrEP; this indication is not addressed in the Pediatric Antiretroviral Guidelines.</li> </ul> <p><b>[Cabenuva] CAB and Rilpivirine (RPV) for IM Injection (Long-Acting Injectable CAB and RPV)</b></p> <p><i>Pediatric Dose</i></p> <ul style="list-style-type: none"> <li>CAB tablets and co-packaged long-acting injectable CAB and RPV are not FDA approved for the treatment of HIV in children aged &lt;12 years.</li> </ul>	<ul style="list-style-type: none"> <li>Depression</li> <li>Insomnia</li> <li>Headache</li> <li>Rash (can be severe and include drug reaction with eosinophilia and systemic symptoms) or hypersensitivity</li> <li>Hepatotoxicity</li> <li>Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance</li> <li>Injection site reactions</li> <li>Creatine phosphokinase elevation following IM injection</li> <li>Weight gain</li> </ul>

<p><i>Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• CAB and RPV is a two-drug co-packaged product for IM injection that is FDA approved as a complete regimen for the treatment of HIV-1 in patients with HIV RNA levels &lt;50 copies/mL on a stable antiretroviral (ARV) regimen with no history of treatment failure and no known or suspected resistance to CAB or RPV.</li> <li>• Oral lead-in dosing with CAB and RPV for at least 28 days can be used to assess tolerability prior to initiating long-acting injectable CAB and RPV injections, or patients can proceed directly to long-acting injectable CAB and RPV on the last day of their current ARV regimen.</li> <li>• Refer to the package insert for instructions about changing the frequency of IM injections, i.e., from monthly to every-2-month dosing or from every-2-month to monthly dosing.</li> </ul> <p><b>Oral Lead-in Dosing</b></p> <ul style="list-style-type: none"> <li>○ CAB 30 mg orally and RPV 25 mg orally once daily with a meal for at least 28 days.</li> </ul> <p><b>Dosing for Monthly Administration of Long-Acting Injectable CAB and RPV</b></p> <ul style="list-style-type: none"> <li>○ On the last day of oral lead-in therapy or the current oral ARV regimen, a loading dose of CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites.</li> <li>○ Continuation therapy of CAB 400 mg (2 mL) and RPV 600 mg (2 mL) IM is given 1 month after the loading dose and once a month thereafter, with allowance for a ±7-day administration window.</li> </ul> <p><b>Dosing for Every-2-Month Administration of Long-Acting Injectable CAB and RPV</b></p> <ul style="list-style-type: none"> <li>○ To initiate every-2-month dosing, CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites on the last day of oral lead-in or the current oral ARV regimen and 1 month after the initial injections.</li> <li>○ After these two initiation injections 1 month apart for 2 months, continuation therapy with IM CAB 600 mg (3 mL) and RPV 900 mg (3 mL) is administered every 2 months, with allowance for a ±7-day administration window.</li> </ul> <p>Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles (not included with packaging) should be used in patients with a body mass index &gt;30 kg/m<sup>2</sup>. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that providers review instructions available</p>	<p style="text-align: center;"><b>Special Instructions</b></p> <ul style="list-style-type: none"> <li>• Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV. Refer to the RPV package insert for specific instructions regarding use of these products during the oral lead-in dosing.</li> <li>• If monthly injections are missed or delayed by more than 7 days and oral therapy has not been taken, clinically reassess the patient to determine if resumption of injection dosing remains appropriate. Refer to the package insert for information about managing planned and unplanned missed doses.</li> <li>• Long-acting injectable CAB and RPV is a complete regimen. Coadministration with other ARV drugs is not recommended.</li> <li>• When long-acting injectable CAB and RPV injections are stopped, residual concentrations may remain measurable for up to 12 months or longer. It is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of long-acting injectable CAB and RPV.</li> <li>• Use CAB and RPV with caution when coadministering with a drug that has a known risk of prolonging the QT corrected for heart rate interval or causing Torsades de Pointes (for more information, see <a href="#">CredibleMeds</a>).</li> </ul> <p style="text-align: center;"><b>Metabolism/Elimination</b></p> <ul style="list-style-type: none"> <li>• CAB is metabolized by uridine diphosphate-glucuronosyl transferase 1A1.</li> <li>• RPV is a cytochrome P450 3A substrate.</li> </ul> <p><b>Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>• No dose adjustment of CAB or long-acting injectable CAB and RPV is necessary in patients with mild or moderate hepatic impairment.</li> </ul> <p><b>Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.</li> <li>• No dose adjustment of CAB or long-acting injectable CAB and RPV is necessary in patients with mild or moderate renal impairment. However, long-acting injectable CAB and RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events.</li> </ul>
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with the package insert prior to beginning IM administration of long-acting injectable CAB and RPV. <a href="#">Additional clinical resources, including injection education, are available from the manufacturer, ViiV.</a>	
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Cabotegravir (CAB) is metabolized primarily by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). **CAB is contraindicated in patients receiving** strong inducers of UGT1A1 because such inducers **decrease CAB plasma concentrations** which may result in **a loss of virologic response**.
- Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate, and RPV concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before CAB plus RPV is administered.
- CAB and RPV are both highly protein bound and unlikely to be removed by hemodialysis.
- Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
  - Antacids should not be taken 2 hours before or 4 hours after oral RPV.
  - H2 receptor antagonists should not be administered 12 hours before or 4 hours after oral RPV.
  - Oral RPV **is contraindicated** with proton pump inhibitors.
- Rifamycin drugs significantly reduce CAB and RPV plasma concentrations. For patients who are concomitantly receiving rifabutin and oral RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal. Coadministration of the following drugs **is contraindicated**:
  - Rifampin and oral RPV
  - Rifampin or rifapentine and CAB
  - Rifabutin and long-acting injectable CAB and RPV

## Major Toxicities

- *More common:* Injection site reactions, insomnia, headache, rash, elevated creatine phosphokinase serum concentrations
- *More common:* In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotrophic hormone stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 of 30 patients (20%) developed this abnormality.<sup>1</sup> The clinical significance of these results is unknown.
- *Less common (more severe):* Depression or mood changes, suicidal ideation

- *Rare:* Hepatotoxicity and post-injection reactions, including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure
- *Rare:* RPV drug-induced liver injury has been reported.<sup>2</sup>

## 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*

CAB oral tablets (Vocabria) and co-packaged long-acting injectable CAB and RPV (Cabenuva) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV in children or adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg (2022) and adults (2021). They are not approved for use in children aged  $< 12$  years. CAB tablets were approved by the FDA in 2021 for use in adults as part of the oral lead-in prior to beginning long-acting injectable CAB and RPV or as an oral interim treatment when patients miss planned injections.<sup>1,3</sup> CAB and RPV co-packaged extended-release injectable suspensions for IM use are approved for use in patients (monthly or every 2 months) who are virologically suppressed on a stable antiretroviral (ARV) regimen with no history of virologic failure or known resistance affecting either of the component drugs.<sup>1</sup>

In December 2021, the FDA approved CAB IM (Apretude) for HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing at least 35 kg; an oral lead-in period of approximately 1 month may be used to assess safety and tolerability but is optional. Refer to the package insert for additional information about dosing and administration,<sup>4</sup> and see the Centers for Disease Control and Prevention [Guidelines for Pre-Exposure Prophylaxis for the Prevention of HIV in the United States](#) for further information about the use of CAB for PrEP.

### *Efficacy and Pharmacokinetics in Clinical Trials*

#### **Clinical Trials in Pediatric Patients 12 Years to $< 18$ Years**

The safety and efficacy of CAB, an HIV-1 integrase inhibitor, given in combination with RPV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been characterized in a series of clinical trials conducted in adults, which form the basis for approval.

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Study 2017, More Options for Children and Adolescents (MOCHA), is currently in progress to evaluate the safety, tolerability, acceptability, and pharmacokinetics of this injectable regimen in adolescents ([MOCHA Trial](#)) and has reported initial results leading to FDA approval in this age group. MOCHA evaluated 23 virologically suppressed adolescents on stable therapy who received either a 4-week lead-in of oral CAB followed by IM CAB 600 mg at Week 4 and 400 mg at Weeks 8 and 12 (n = 8) or a lead-in of oral RPV followed by IM RPV 900 mg at Week 4 and 600 mg at Weeks 8 and 12 (n = 13). Injection site reactions were observed but **did not lead to** treatment discontinuations. Two adolescents experienced Grade 3 adverse events, one due to insomnia (CAB arm) and one due to hypersensitivity

reaction to oral RPV, which led to discontinuation.<sup>5</sup> In a concurrent assessment of adolescent and parental experiences with IM treatment in MOCHA, overall perceptions of the injectable treatment were favorable. Of the 21 adolescents who received all three study injections, >90% “definitely” or “probably” wanted to continue IM treatment.<sup>6</sup> It should be noted, however, that none of the MOCHA participants received both monthly IM CAB and monthly IM RPV as a dual complete regimen, and clinical experience with this product remains limited. **Intermittent viremias have been reported in young adults transitioned to long-acting injectable CAB and RPV with oral lead-in.**<sup>7</sup> The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV notes that significant questions remain regarding the use of long-acting injectable CAB and RPV in pediatric patients, including whether an oral lead-in is beneficial in the adolescent population, whether there are additional adverse effects specific to the pediatric population, whether the use of a two-drug nucleoside-sparing regimen for children with significant ARV treatment history is appropriate, and what potential implementation challenges might exist.

### **Clinical Trials in Adults**

The Phase 3 Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study randomized stable, virologically suppressed adults to receive either CAB and RPV (n = 308) or continue their oral antiretroviral therapy (ART) (n = 308). Patients assigned to CAB and RPV initiated therapy with an oral regimen for 4 weeks prior to beginning monthly IM injections. The initial assessment at 48 weeks demonstrated that switching to monthly long-acting injectable CAB and RPV was noninferior to continuing a three-drug oral therapy. After 48 weeks, participants were allowed to transition to injections every 2 months in a follow-up study (ATLAS-2M, see below); 52 patients remaining on the original ATLAS study were included in the 96-week analysis. Adverse events were more common among patients receiving injectable ART; injection site reactions were common, but only 1% withdrew from the study because of these events.<sup>8</sup> The ATLAS-2M trial randomized participants to monthly IM CAB 400 mg and RPV 600 mg (n = 523) or every-2-month injections of CAB 600 mg and RPV 900 mg (n = 522); it enrolled both new patients and those continuing from the ATLAS trial. After 96 weeks, the every-2-month injections were noninferior to monthly injections, with 11 (2%) confirmed virologic failures in the every-2-month injection group and 6 (1%) in the monthly injection group. No new safety signals were identified, and the rate of injection site reactions—the most common adverse event—was similar across treatment arms. Of those failing the every-2-month injection regimen, a majority had NNRTI resistance-associated mutations.<sup>9</sup>

The First Long-Acting Injectable Regimen (FLAIR) study enrolled 631 treatment-naïve adults and initiated treatment with a standard oral ARV regimen consisting of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) for 20 weeks. Those patients with documented HIV-1 RNA <50 copies/mL after 16 weeks were randomized to either continue oral DTG/ABC/3TC (n = 283) or switch to oral CAB and RPV for 4 weeks, followed by monthly injections of CAB and RPV (n = 283). After 96 weeks of randomized therapy, nine participants (3.2%) in each arm had HIV RNA >50 copies/mL. Adverse events were common in both treatment groups, but adverse events leading to withdrawal from the study were observed in only 14 (5%) participants in the long-acting injectable CAB and RPV group and 4 (1%) in the oral standard care group. Injection site reactions were the most common adverse events, reported by 245 (88%) participants in the long-acting injectable CAB and RPV group, and lasted a median of 3 days.<sup>10</sup> The FLAIR study was extended to include an assessment of switching those participants remaining in the oral ARV arm after 120 weeks to long-acting injectable CAB and RPV either with or without the initial oral lead-in phase. There were no differences between the lead-in group and the direct-to-injection group in terms of safety, tolerability, or efficacy through an additional 24 weeks on the study.<sup>11</sup>

These studies demonstrated noninferiority of switching to monthly long-acting injectable CAB and RPV compared to continuing oral ART. In all studies, adult patients expressed a high degree of treatment satisfaction and preference for the long-acting injectable CAB and RPV regimen. Although documented virologic failure with the long-acting injectable CAB and RPV regimen has been rare to date, investigators have attempted to assess the baseline factors associated with treatment failure. In a multivariate analysis of the adult long-acting injectable CAB and RPV Phase 3 trials, presence of at least two baseline factors of RPV resistance-associated mutations, HIV-1 subtype A6/A1, and body mass index  $>30\text{kg/m}^2$  was associated with increased risk of virologic failure at 48 weeks.<sup>12</sup>

### ***Pharmacokinetics***

The pharmacokinetics (PK) of IM CAB are driven by slow absorption from the injection site. IM CAB reaches its maximum plasma concentration in adults in about 7 days and has a mean half-life of 5.6 to 11.5 weeks. Measurable levels of CAB can be detected in plasma for up to a year or longer. Due to this prolonged drug exposure, it is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of CAB and RPV to minimize the potential risk of developing viral resistance.<sup>1</sup> The PK profiles observed in adolescents enrolled in MOCHA were comparable to those observed in adults receiving monthly long-acting injectable CAB and RPV in the ATLAS and FLAIR studies described above.<sup>5</sup>



## Dolutegravir (DTG, Tivicay, Tivicay PD)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p><b>Tablets</b></p> <ul style="list-style-type: none"> <li>Dispersible tablets for oral suspension [Tivicay PD] 5 mg</li> <li>Film-coated tablets [Tivicay] 10 mg, 25 mg, 50 mg</li> </ul> <p><b>Fixed-Dose Combination Tablets</b></p> <ul style="list-style-type: none"> <li>[Dovato] Dolutegravir 50 mg/lamivudine 300 mg</li> <li>[Juluca] Dolutegravir 50 mg/rilpivirine 25 mg</li> <li>[Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg</li> <li>[Triumeq PD] Abacavir 60 mg/dolutegravir 5 mg/lamivudine 30 mg</li> </ul> <p>When using fixed-dose combination (FDC) tablets, refer to other sections of <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p>All formulations and FDCs of dolutegravir (DTG) are U.S. Food and Drug Administration (FDA)–approved for use in treatment-naïve or treatment-experienced pediatric, adolescent, and adult patients naïve to the integrase strand transfer inhibitor (INSTI) drug class. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV endorses the use of DTG as appropriate for some children with prior INSTI use (see <a href="#">Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy and Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy</a>).</p> <p><b>Neonate Dose</b></p> <ul style="list-style-type: none"> <li>DTG is not approved by the FDA for use in neonates.</li> </ul>	<ul style="list-style-type: none"> <li>Insomnia</li> <li>Headache</li> <li>Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness</li> <li>Rare cases of hypersensitivity reactions (HSRs), including rash and <b>DRESS</b> (drug reaction [or rash] with eosinophilia and systemic symptoms), constitutional symptoms, and organ dysfunction (including liver injury)</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>DTG may be taken <b>with or</b> without food.</li> <li>DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.</li> </ul>



**[Tivicay PD] DTG Dispersible Tablets**

*Infant (Aged ≥4 Weeks and Weighing ≥3 kg), Child, and Adolescent Dose*

Pediatric Body Weight	Recommended Dose <sup>a</sup> of Dolutegravir Dispersible Tablets	Number of 5-mg Tablets
3 kg to <6 kg	5 mg once daily	1
6 kg to <10 kg	15 mg once daily	3
10 kg to <14 kg	20 mg once daily	4
14 kg to <20 kg	25 mg once daily	5
≥20 kg	30 mg once daily	6

<sup>a</sup> If certain drugs that induce uridine diphosphate glucuronyl transferase (UGT) 1A or cytochrome P450 (CYP) 3A are coadministered, administer DTG dispersible tablets twice daily (see the Drug Interactions section below).

**[Tivicay] DTG Film-Coated Tablets**

*Child and Adolescent (Weighing ≥14 kg) Dose*

- DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Each formulation has different doses.

**Dosing of Film-Coated Tablets for Pediatric Patients Weighing ≥14 kg Who Can Swallow Tablets**

Pediatric Body Weight	Recommended Dose <sup>a</sup> of DTG Film-Coated Tablets	Number of Tablets
14 kg to <20 kg	40 mg once daily	4 x 10 mg
≥20 kg	50 mg once daily	1 x 50 mg

<sup>a</sup> If certain drugs that induce UGT1A or CYP3A are coadministered, administer DTG tablets twice daily (see the Drug Interactions section below).

Some infants may have received raltegravir as presumptive HIV therapy prior to diagnosis. These infants and other infants and children with HIV who have received INSTIs are candidates to switch to once-daily DTG if they are virologically suppressed or have no mutations associated with resistance to INSTIs.

*Adult Dose*

- One 50-mg DTG film-coated tablet once daily
- If certain drugs that induce UGT1A or CYP3A are coadministered, administer DTG 50 mg twice daily (see the Drug Interactions section below).

- For DTG dispersible tablets, fully disperse the dispersible tablets in 5 mL of drinking water (if using one or three tablets) or in 10 mL of drinking water (if using four, five, or six tablets) in the supplied cup; swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure the child takes the full dose and no medication remains in the dosing cup.
- DTG dispersible tablets may be swallowed whole. If more than one tablet is required, swallow one tablet at a time to reduce the risk of choking. DTG dispersible tablets should not be chewed or crushed.
- For ABC/DTG/3TC dispersible tablets, **tablets should be fully dispersed in the appropriate volume** of drinking water in the supplied cup and the suspension should be swirled so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water and give this additional water to the child to ensure the child takes the full dose and no medication remains in the dosing cup. ABC/DTG/3TC dispersible tablets should not be swallowed whole, chewed, or crushed.
- No data exist regarding dispersion in breast milk or any vehicles other than water.
- In patients who have difficulty swallowing the film-coated tablets whole, 50-mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.<sup>1</sup>
- The efficacy of DTG is reduced in patients with certain combinations of INSTI-resistance mutations. **DTG dosing strategies in pediatric patients with first-generation INSTI mutations differ from those in adults (see Table A and the Resistance section below).** Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain 3TC. Severe acute exacerbations of HBV can occur after discontinuation of 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.
- For any FDC tablets containing ABC, test patients for the HLA-B\*5701 allele before starting therapy to predict the risk of HSRs. Patients who test positive for the HLA-B\*5701 allele should not be given an ABC-containing FDC. Patients with no prior HLA-B\*5701 testing who are tolerating an ABC-containing regimen do not need to be tested. See the [Abacavir](#) section.

- Adults who are INSTI-experienced with certain INSTI-associated resistance mutations or clinically suspected INSTI resistance should receive 50 mg DTG twice daily.

**[Dovato] DTG/Lamivudine (3TC)**

**Adolescents Aged ≥12 Years and Weighing ≥25 kg and Adult Dose**

- One tablet once daily with or without food as a complete regimen in antiretroviral (ARV)-naive adolescents with no known mutations associated with resistance to the individual components of Dovato

**[Juluca] DTG/Rilpivirine**

**Adult Dose**

- One tablet once daily with a meal as a complete regimen 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 mutations associated with resistance to the individual components of Juluca

**[Triumeq PD] Abacavir (ABC)/DTG/3TC**

**Children Aged ≥3 Months and Weighing ≥6 kg to <25 kg**

- Dispersible Triumeq PD tablets are FDA approved for children weighing ≥6 to <25 kg. They are not recommended for children weighing ≥25 kg.
- Administer the appropriate number of tablets for a child's weight once daily. Tablets should be dispersed in 15 mL of water if using three tablets or 20 mL of water if using four to six tablets, see Special Instructions. Triumeq PD tablets should not be swallowed whole, chewed, cut, or crushed.

**Weight-Band Dosing of Triumeq PD Tablets for Children Aged ≥3 Months and Weighing ≥6 kg**

Weight	Recommended Daily Dose	Number of Triumeq PD Tablets
6 kg to <10 kg	ABC 180 mg, DTG 15 mg, 3TC 90 mg	3
10 kg to <14 kg	ABC 240 mg, DTG 20 mg, 3TC 120 mg	4
14 kg to <20 kg	ABC 300 mg, DTG 25 mg, 3TC 150 mg	5
20 kg to <25 kg	ABC 360 mg, DTG 30 mg, 3TC 180 mg	6
≥25 kg	Use Triumeq. See below.	

**Metabolism/Elimination**

- Substrate for UGT1A1 and CYP3A. Also, a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) *in vitro*. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes or transporters may increase DTG plasma concentrations.

**DTG Dosing in Patients with Hepatic Impairment**

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to the lack of data, DTG is not recommended for use in patients with severe hepatic impairment.
- FDC tablets containing ABC or 3TC should not be used in patients with impaired hepatic function.

**DTG Dosing in Patients with Renal Impairment**

- DTG decreases tubular secretion of creatinine and increases measured serum creatinine without affecting glomerular filtration.
- No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.
- FDC tablets containing 3TC (Dovato, Triumeq PD, and Triumeq) should not be used in patients who have CrCl <30 mL/min or patients who are on dialysis because the doses of 3TC cannot be adjusted. Data about the FDC DTG/3TC (Dovato) suggest that patients with a sustained creatinine clearance 30–49 mL/min may experience a higher 3TC exposure and should be monitored for hematologic toxicities and potential FDC discontinuation and subsequent adjustment of the treatment regimen. See package inserts for additional information.

<ul style="list-style-type: none"> <li>• For use in patients who are ARV naive or ARV experienced (but INSTI naive) and who are not being treated with UGT1A1 or CYP3A inducers</li> <li>• See the <a href="#">Abacavir</a> section for special instructions about testing for ABC hypersensitivity.</li> </ul> <p>[Triumeq] ABC/DTG/3TC</p> <p><i>Child and Adolescent (Weighing ≥25 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>• One tablet once daily with or without food</li> <li>• For use in patients who are ARV naive or ARV experienced (but INSTI naive) and who are not being treated with UGT1A1 or CYP3A inducers</li> <li>• See the <a href="#">Abacavir</a> section for special instructions about testing for ABC hypersensitivity.</li> </ul>	
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. DTG dosing should be adjusted to twice daily (i.e., twice the usual dose) when coadministered with drugs such as efavirenz and rifampin.<sup>2-4</sup> Because etravirine (ETR) significantly reduces plasma concentrations of DTG, DTG **should not be administered** with ETR without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on DTG concentrations. DTG **should not be administered** with nevirapine because of insufficient data on interactions between these drugs. See the product label for a full listing of significant drug–drug interactions.
- Atazanavir (ATV) is an inhibitor of UGT1A1. In a pharmacologic survey of adult patients who were receiving DTG, patients who also received ATV had plasma concentrations of DTG that were twofold to fourfold higher than those of patients who received other antiretroviral (ARV) drugs.<sup>5</sup>
- Before administering DTG, clinicians should carefully review a patient’s medication profile for potential drug interactions.

## Major Toxicities

- *More common:* Insomnia and headache. Weight gain and increased body mass index (BMI) have been reported in adults who received DTG in clinical trials and in some pediatric and adolescent cohorts (see [Table 17h. Lypodystrophies and Weight Gain](#)).<sup>6-9</sup>
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional symptoms, and sometimes organ dysfunction; neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple postmarketing reports note that neuropsychiatric adverse events (AEs) have occurred following the initiation of DTG-based therapy in adults.<sup>10,11</sup>

- *Immune reconstitution inflammatory syndrome (IRIS)*: In retrospective observational studies, severe cases of IRIS that required hospitalization appeared to be more frequent in patients who presented with advanced HIV disease and who initiated treatment with integrase strand transfer inhibitors (INSTIs), particularly DTG.<sup>12,13</sup> This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving INSTI-based therapy.
- *Rare*: Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of DTG. One of these cases required liver transplantation.<sup>14,15</sup>
- *Rare*: A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.<sup>16</sup>

## Resistance

The International Antiviral Society–USA maintains a [list of updated resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

The efficacy of DTG is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations, and this reduced efficacy cannot be completely overcome with increasing DTG dosing.<sup>17,18</sup>

For adults with first-generation INSTI-resistance mutations, the package insert recommends doubling the DTG dose and give the standard dose twice daily rather than once daily. However, modeling and simulation of this strategy with the dispersible tablet formulation of DTG in children suggested elevated maximum plasma concentrations ( $C_{max}$ ) in comparison to historical data in adults, adolescents, and children would result. Thus, a different dosing strategy was needed for children with first-generation INSTI-resistance mutations. The proposed dosing schedule in Table A below was based on simulations with the goal of achieving geometric mean concentration at 12 hours postdose  $>1.97 \mu\text{g/mL}$  and area under the curve (AUC) through 12 hours postdose  $>32.2 \mu\text{g}\cdot\text{h/mL}$  while avoiding elevated  $C_{max}$  values.<sup>19</sup> Additionally, the coformulated dispersible tablet containing abacavir (ABC)/DTG/lamivudine (3TC) cannot be used in combination with a separate dose of single-agent dispersible release DTG because the dosing of the separate formulation is not double the regular dose and the modified dosing strategy would result in underdosing the ABC and 3TC components.

**Table A. Weight-Band Dosing of Dolutegravir Dispersible Tablets for Pediatric Patients Weighing  $\geq 3$  kg and Aged  $\geq 3$  Months with First-Generation INSTI-Resistance Mutations**

Weight	Recommended Twice Daily Dose	Number of Tablets per Dose
3 kg to <6 kg	5 mg	1
6 kg to <10 kg	10 mg	2
10 kg to <14 kg	15 mg	3
14 kg to <20 kg	15 mg	3
20 kg to <30 kg	20 mg	4
30 kg to <40 kg	20 mg	4

## Pediatric Use

### *Approval*

DTG is approved by the FDA for use, in combination with other ARV drugs, in pediatric patients aged at least 4 weeks and weighing  $\geq 3$  kg who are treatment naive or treatment experienced but INSTI naive (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](#)). DTG dispersible tablets and film-coated tablets in either the single-entity or fixed-dose combination (FDC) form can be administered with or without food.<sup>20,21</sup> Pediatric patients weighing  $\geq 20$  kg may take the DTG 50-mg film-coated tablets if they are able to swallow tablets. The combination tablet ABC/DTG/3TC (Triumeq) is approved by the FDA for use in children and adolescents weighing  $\geq 25$  kg. Dispersible ABC/DTG/3TC tablets (Triumeq PD) are FDA approved for use in children weighing  $\geq 10$  kg to  $< 25$  kg. The combination tablet DTG/3TC (Dovato) is approved by the FDA for adolescents weighing  $\geq 25$  kg and aged  $\geq 12$  years but is not approved for use in children aged  $< 12$  years. The combination tablet DTG/rilpivirine (RPV) (Juluca) is not approved by the FDA for use in children or adolescents.

### *Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet*

DTG is currently available as either film-coated tablets or dispersible tablets (tablets for oral suspension). The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,<sup>22</sup> so recommended doses using the dispersible tablet cannot be directly compared to those using the film-coated tablets. The drug exposure provided by the 50-mg film-coated tablet is approximately equal to that of DTG 30 mg administered as dispersible tablets.

## Efficacy and Pharmacokinetics

### *Pediatric Patients Aged 4 Weeks to <18 Years*

[IMPAACT P1093](#) is an ongoing, multinational, open-label trial of DTG in children with HIV. Results of pharmacokinetic (PK), safety, and efficacy assessments have been reported sequentially for different age and weight cohorts as data became available; similarly, dosing recommendations have been revised sequentially.<sup>23-25</sup> Dosing recommendations that previously included the 25-mg film-coated tablets have been replaced with other formulations.

Data from IMPAACT P1093 Cohort 1 (aged 12 years to  $< 18$  years) and Cohort 2 (6 years to  $< 12$  years) provide support for use of DTG film-coated tablets in pediatric patients weighing  $\geq 14$  kg; Cohort 3 (2 to  $< 6$  years), Cohort 4 (6 months to  $< 2$  years), and Cohort 5 (4 weeks to  $< 6$  months) provide evidence supporting the use of DTG 5-mg dispersible tablets. Seventy-five study participants ranging in age from 1 month to 214 months received the currently approved dose (determined by weight and age) of DTG film-coated tablets or dispersible tablets. Eighty percent of participants were treatment experienced, but all were INSTI naive. Among these 75 patients who received either DTG film-coated tablets or DTG dispersible tablets, according to the approved dosing recommendations for their weight band, 42 received DTG for at least 48 weeks. At Week 48, 69% of participants achieved HIV RNA  $< 50$  copies/mL, and 79% achieved HIV RNA  $< 400$  copies/mL. The median CD4 T lymphocyte cell (CD4) count (percent) increase from baseline to Week 48 was 141 cells/mm<sup>3</sup> (7%). Overall, the safety profile in P1093 participants was comparable to that observed in adults, and



both formulations were well tolerated by pediatric patients. The effectiveness observed in the trial was comparable to that of treatment-experienced adult participants.<sup>26</sup>

Sixteen adolescents in Cohort 1 remained on P1093 through 144 weeks, with 43% and 35% of participants achieving and maintaining HIV RNA levels <400 copies/mL and <50 copies/mL, respectively. Genotypic testing was available at the time of treatment failure for 6 of the 13 participants experiencing treatment failure; one of these adolescents developed DTG resistance.<sup>27</sup>

A subsequent analysis of a larger group of 73 participants in Cohorts 3 through 5 (4 weeks to <6 years of age), who received the final proposed dose and of whom 87.7% were treatment experienced, confirmed safety as assessed to 48 weeks with no Grade 3 or higher AEs attributed to DTG. Of 68 participants with HIV RNA data at 48 weeks, 91% and 68% achieved HIV RNA <400 copies/mL and <50 copies/mL, respectively.<sup>25</sup>

The Once-daily DTG-based ART in Young people vS Standard thErapY (ODYSSEY) trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA), enrolled both treatment-naïve and treatment-experienced pediatric patients from the European Union, Thailand, and several African countries; this trial initially evaluated doses approved by the European Medicines Agency at the time the trial started. A total of 707 children aged <18 years were enrolled; 311 children started DTG as first-line therapy, and 396 started DTG as second-line therapy.<sup>28</sup> As assessed by 96 weeks, DTG-based ART as both first-line therapy and second-line therapy in children was superior to standard care.<sup>29</sup> Results from the younger ODYSSEY cohort of children weighing between 3 and 14 kilograms showed superiority of DTG-based ART compared to other regimens, of which over 70% were protease inhibitor (PI)-based regimens.<sup>29-31</sup>

Nested PK substudies within ODYSSEY also evaluated simplified pediatric dosing that aligned with the World Health Organization's (WHO) recommended weight bands. PK data are available from a cohort of children weighing >25 kg who switched to the DTG 50-mg film-coated tablet. Data from another ODYSSEY cohort reported on children weighing 20 kg to <25 kg who received either the DTG 50-mg film-coated tablet or DTG 30 mg administered as six 5-mg dispersible tablets. Both of these doses achieved AUC and maximum plasma concentration ( $C_{max}$ ) values that were higher than adult PK reference values but still acceptable. Both doses achieved trough plasma concentration values that were slightly lower than adult reference values and exhibited greater variability but were determined to be acceptable.<sup>32</sup> Later-enrolling ODYSSEY cohorts included children weighing 3 kg to <20 kg.<sup>33</sup> Children weighing 14 kg to <20 kg received 25 mg and were enrolled first, then children weighing 3 kg to <6 kg and younger than 6 months received 5 mg DTG, 3 kg to <6 kg and older than 6 months received 10 mg, 6 kg to <10 kg received 15 mg, and 10 kg to <14 kg received 20 mg. For all weight bands, the DTG **AUC through 24 hours post-dose** was comparable to or higher than the target values in adults receiving the approved dose but within an acceptable safety margin. A total of 19 children weighing <20 kg experienced Grade 3 or higher AEs, including two deaths (one kwashiorkor and one accidental trauma) assessed as unrelated to the study drug. Eleven participants experienced serious AEs, 69% of which were due to infectious diseases. Long-term safety and effectiveness assessments in the ODYSSEY trial are ongoing.

Combined PK data from P1093 and ODYSSEY across all age/weight cohorts form the basis for the current FDA dose recommendations and are summarized in [Table B](#) below. These data support the administration of either 30 mg as dispersible tablets or 50 mg as a film-coated tablet in patients weighing  $\geq 20$  kg. In addition, modeling and simulations that included UGT1A1 maturation in infants were used to support the dose of DTG in infants at least 4 weeks of age and weighing at least 3 kg.

Separate PK studies have continued to support adequate DTG exposures among children and adolescents at the currently recommended doses.<sup>20,34,35</sup> Dosing in neonates is under investigation.

**Table B: Summary of Pharmacokinetic Parameters in Pediatric Participants with HIV-1 (Pooled Analyses for IMPAACT P1093 and ODYSSEY Trials)**

Weight Band <sup>a</sup>	Dose <sup>b</sup> of DTG FCT or DTG DT	n	Pharmacokinetic Parameter Geometric Mean (% CV)		
			C <sub>max</sub> (mcg/mL)	AUC <sub>0-24h</sub> (mcg·h/mL)	C <sub>24h</sub> (ng/mL)
3 kg to <6 kg	DTG DT 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	DTG DT 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to <14 kg	DTG DT 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to <20 kg	DTG DT 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	DTG DT 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	DTG FCT 50 mg once daily	49	4.92 (40)	54.98 (43)	778 (62)
Adults <sup>c</sup>	DTG FCT 50 mg once daily		3.67 (20)	53.6 (27)	1,110 (46)
Adults <sup>c</sup>	DTG FCT 50 mg twice daily		4.15 (29)	75.1 (35)	2,120 (47)

<sup>a</sup> Data are from two weight-band-based pharmacokinetic substudies in the ODYSSEY trial.

<sup>b</sup> The bioavailability of DTG tablets for oral suspension is approximately 1.6-fold that of DTG film-coated tablets.

<sup>c</sup> Adult pharmacokinetic data are based on population pharmacokinetic analyses from clinical trials.<sup>26</sup>

**Key:** AUC<sub>0-24h</sub> = 24-hour area under the curve; C<sub>24h</sub> = concentration at 24 hours postdose; C<sub>max</sub> = maximum plasma concentration; CV = coefficient of variation; DT = dispersible tablets; DTG = dolutegravir; FCT = film-coated tablets

Efficacy and safety of DTG-based regimens have been evaluated in multiple observational pediatric cohorts. Additional long-term efficacy and safety data for this age/weight group come from a retrospective, multicenter French cohort study that evaluated 134 children and adolescents who received DTG-based ART for at least 12 months. Most participants were ART experienced (90.3%) but integrase inhibitor naive (90.3%) and had virologic suppression at baseline (63.4%).<sup>36</sup> Virologic failure occurred in 43 participants (32%) and occurred more frequently when baseline viral load was ≥50 copies/mL (67.4% vs. 22.0%, *P* < 0.01). Resistance mutations to DTG emerged in one patient with virologic failure.<sup>36</sup> Retrospective analyses of children and adolescents aged ≤19 years and weighing ≥20 kg have also been performed from DTG rollout programs across Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda.<sup>37</sup> Of the 9,419 children and adolescents who initiated DTG between 2017 and 2020, 73% received tenofovir disoproxil fumarate (TDF)/3TC/DTG, 24% received ABC/DTG/3TC, and 3% received zidovudine/3TC/DTG. Only 0.7% reported a toxicity that resulted



in DTG discontinuation. Virologic suppression was documented in 92.7% (8,273 of 8,921) before switching to DTG. Following the switch, 93.4% (7,378 of 7,898) on DTG had documented virologic suppression, including 79.8% (426 of 534) of those not previously suppressed on their original regimen. However, the analysis did not include data for comparison among participants who were not suppressed and did not switch to a DTG-containing regimen. Factors associated with increased odds of virologic suppression included being virologically suppressed prior to ART switch (odds ratio [OR] 3.87; 95% confidence interval [CI], 3.03–4.95) and use of once-daily TDF/3TC/DTG as a single-tablet regimen (OR 1.78; 95% CI, 1.43–2.22), whereas age increases were associated with slightly reduced odds of virologic suppression (OR 0.94 for each 1-year increase; 95% CI, 0.91–0.97). A separate report among 3,347 children aged <14 years receiving DTG as part of a national rollout program in southern Mozambique revealed virologic suppression rates of 79.7% (63 of 79) in children newly initiating DTG and 85.8% (1,775 of 2,068) in those switching to DTG.<sup>38</sup> However, more than one-third experienced at least two regimen changes during the follow-up period from 2019 to 2021, some of which involved switching from DTG to either a PI or non-nucleoside reverse transcriptase inhibitor (NNRTI). These changes were attributable, in part, to drug shortage, illustrating the importance of continued access and supply of DTG to support rollout initiatives.

Although observational studies have shown high virologic suppression rates, emerging INSTI mutations specific to DTG have been reported among children being monitored in national treatment programs, as opposed to observational studies. Thus, continued assessments of virologic suppression longer term and the development of resistance will be important.<sup>39,40</sup>

The PK, safety, tolerability, and efficacy of dispersible and immediate-release FDC tablet formulations of ABC/DTG/3TC were investigated in children weighing 6 kg to <40 kg and aged <12 years among 57 children enrolled in the IMPAACT 2019 study.<sup>41</sup> Children were dosed across five weight bands in alignment with the WHO ARV dosing recommendations for each component. Children weighing 6 kg to <25 kg received the dispersible FDC formulation containing ABC 60 mg/DTG 5 mg/3TC 30 mg (Triumeq PD), and those weighing 25 to <40 kg received the immediate-release FDC formulation containing ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Drug exposures for all three components were comparable to previous studies in children and adults with HIV, including DTG exposures from IMPAACT P1093 and ODYSSEY. Dosing was confirmed based on PK and safety criteria across all weight bands in alignment with WHO weight-band dosing recommendations. Data available through 24 weeks of treatment showed there were no Grade 3 or 4 AEs related to the drug components, and no participant discontinued the study drug because of AEs. At Week 24, 54 of 57 (95%) of participants were suppressed to <200 copies/mL, and all treatment-experienced patients who switched to ABC/DTG/3TC maintained suppression. Both formulations were also well tolerated, and 10 of 11 participants in the highest weight band were able to swallow the larger immediate-release tablet whole and intact (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](#)). Analyses of safety and efficacy data through 48 weeks are ongoing.

A separate cohort of adolescents in Barcelona, Spain, received the immediate-release FDC ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the 12 patients described, 1 was treatment naive, 6 were undergoing treatment simplification, and 5 had previously experienced virologic failure on a different ART regimen. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients did not achieve suppression because of suboptimal adherence. Of note, patients complained about the size of the tablet, and six patients reported having to crush or split the tablet to swallow it, in contrast to tolerability findings in IMPAACT 2019.<sup>42</sup>

## *Pediatric Postmarketing Safety Studies*

As long-term data are analyzed from the [ODYSSEY trial](#), additional comparative safety information has been reported. The investigators reported a small number of neuropsychiatric AEs in the 707 children and adolescents randomized to DTG, not significantly different from those reported in study participants receiving standard care. However, participants receiving DTG were more likely to have suicidal ideation than those receiving standard care. Suicidal thoughts were reported by 13 participants receiving DTG, but none were reported among those receiving standard care; however, these symptoms were described as transient and did not lead to changes in ART.<sup>30</sup> A separate systematic review of INSTI use in children with perinatal HIV infection identified rates of neuropsychiatric effects from 1% to 16% among those receiving DTG (n=3,448 children).<sup>43</sup>

In a subset of ODYSSEY participants aged 6 to <18 years, no differences were identified in vitamin B12 levels across study arms, although plasma and RBC folate levels were lower among participants receiving standard care.<sup>44</sup>

Reports of weight gain among adults enrolled in clinical trials prompted similar studies to investigate metabolic effects of DTG in adolescents. A group of investigators in Eswatini analyzed BMI measurements retrospectively from a cohort of 460 virally suppressed adolescents switching to a DTG-based regimen (either ABC/DTG/3TC or TDF/3TC/DTG). In this cohort, both weight-for-age z-score and BMI-for-age z-score decreased slightly before transition to DTG but increased during the year after DTG was initiated. The rate of BMI increase per year was calculated to be about twofold greater than the normal rate in the full cohort, and about 2.8-fold greater among female adolescents.<sup>7</sup> A retrospective, single-center study of 97 children and adolescents who received a DTG-based regimen for at least 12 months in France showed that trajectories of BMI z-score change 12 months pre- versus 12 months post-DTG were similar, except in participants with baseline BMI  $\geq$ 50th percentile, whose rate of BMI z-score change was lower post-DTG (difference:  $-0.23$ ;  $P = 0.04$ ).<sup>45</sup> Another group measured multiple body fat parameters and cholesterol/lipid profiles in Italian adolescents switched from a PI- or NNRTI-based regimen to a DTG-based regimen (ABC/DTG/3TC). Although BMI, body fat percentage, and limb fat percentage remained the same, trunk fat and trunk fat/total body fat ratio increased significantly. Total cholesterol and low density lipoproteins decreased, while serum triglycerides decreased early in the study and then increased by the end of the study.<sup>6</sup> A small, single-center cohort in Australia identified similar increases in BMI among adolescents switched to either DTG- or tenofovir alafenamide-containing regimens.<sup>8</sup> Another retrospective analysis of a cohort of children and adolescents in the District of Columbia who were initiated on INSTIs also identified a pattern of increasing BMI-for-age z-scores, with a mean rate of change of  $+0.19$  z-score units per year.<sup>9</sup> The ODYSSEY investigators also assessed weight, height, and BMI over the course of their prospective, randomized study. At Week 96, they found that weight, height, and BMI-for-age z-score increased in children receiving DTG compared with those receiving standard care, with the adjusted difference in means of 1 kg, 0.8 cm, and 0.14 z-score units, respectively. The investigators noted that the differences between treatment groups were relatively small, emerged early, and stabilized within the 2-year study period.<sup>31</sup> A separate study in South Africa showed no significant change in BMI z-score, reduced hepatic steatosis, and lower total cholesterol and triglycerides among 30 adolescents switched to DTG in comparison to those who remained on their original ART regimen, the majority of which were PI-based (84%).<sup>46</sup> Another retrospective study in a Swiss cohort of 60 children with HIV did not identify any significant changes in BMI or BMI standard deviation scores associated with DTG when comparing at 1 year post-DTG switch.<sup>47</sup>

Based on these **collective** data, weight gain may be observed in adolescents receiving DTG, as observed in adults; the long-term clinical significance of these changes are unclear, and further studies are needed in adolescents and children receiving DTG. **See the [What to Start](#) section for additional considerations.**

## Simplification of Treatment

Two trials in adults (Regimen Switch to Dolutegravir + Rilpivirine from Current Antiretroviral Regimen in Human Immunodeficiency Virus Type 1 Infected and Virologically Suppressed Adults [SWORD-1 and SWORD-2]) supported the approval of a DTG 50-mg/RPV 25-mg FDC tablet as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 virologically suppressed patients who had been on stable ART for at least 6 months and who had no history of treatment failure or evidence of resistance mutations. The participants were randomized either to receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA levels <50 copies/mL.<sup>48</sup> After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV. At 148 weeks, 84% of the early-switch patients and 90% of the late-switch patients remained virologically suppressed, and only 11 patients receiving dual therapy met virologic failure criteria. No INSTI-resistance was identified.<sup>49</sup> During the comparative randomized phase of the study, more AEs were reported and led to discontinuation in the DTG/RPV arm. In a subgroup of the SWORD study, small but statistically significant increases in hip and spine bone mineral density and bone turnover markers were observed in patients whose original ARV regimen contained TDF.<sup>50</sup>

The approval of DTG 50 mg/3TC 300 mg as a complete regimen was supported by data from two randomized, double-blind, controlled trials (Efficacy, Safety, and Tolerability Study Comparing Dolutegravir Plus Lamivudine With Dolutegravir Plus Tenofovir/Emtricitabine in Treatment naive HIV Infected Subjects [GEMINI-1 and GEMINI-2]) in ARV-naive adults with HIV. GEMINI-1 and GEMINI-2 are identical 148-week trials that enrolled a total of 1,433 adults with HIV who had plasma HIV RNA levels between 1,000 copies/mL and  $\leq 500,000$  copies/mL at screening and no evidence of major resistance mutations or hepatitis B virus infection. Participants were randomized to receive either DTG plus 3TC or DTG plus 3TC/TDF. During 96 weeks of treatment, 86% of patients who received DTG plus 3TC and 89.5% of patients who received DTG plus 3TC/TDF achieved HIV RNA levels <50 copies/mL. Patients who received DTG plus 3TC had a lower rate of adverse drug reactions (19.6%) than those who received DTG plus 3TC/TDF (25%).<sup>51</sup> **The combination of DTG/3TC was evaluated as initial ART in adolescents weighing  $\geq 25$  kg and aged  $\geq 12$  years to <18 years with baseline HIV-1 RNA between 100 copies/mL and  $\leq 500,000$  copies/mL through the DANCE study. A total of 32 participants were enrolled, of which 81% and 69% achieved HIV RNA levels <50 copies/mL at Weeks 48 and 96, respectively.<sup>52</sup> These results included individuals with missing data due to site closures; thus, sensitivity analyses were performed with the participants excluded. Virologic suppression rates in the sensitivity analyses were 87% (26 of 30) at Week 48 and 88% (22 of 25) at Week 96. Drug exposures for both components were also comparable to historical data in adults and the combination was overall safe and well tolerated.**

Although Juluca is not approved by the FDA for use in adolescents, the doses of the component drugs that make up this FDC tablet is approved for use in adolescents. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. The use of DTG/RPV regimens could be useful in patients in whom there is concern for

toxicity from nucleoside reverse transcriptase inhibitors. However, the Panel notes that adolescents may have difficulties adhering to therapy and suggests considering close monitoring with viral load testing (see the Treatment Simplification section of [Management of Children Receiving Antiretroviral Therapy](#)).

The combination of once-daily darunavir/ritonavir (DRV/r) with an INSTI is being investigated in a randomized non-inferiority trial among virologically suppressed children aged 6 years to <18 years through the SMILE Penta-17-ANRS 152 clinical trial.<sup>53</sup> Participants were randomized to either once-daily DRV/r with an INSTI or continuing their standard-of-care regimen consisting of a boosted PI or NNRTI with a nucleoside reverse transcriptase inhibitor backbone. A total of 318 participants were enrolled between 2016 and 2019, of which 158 were randomized to DRV/r with an INSTI (97% DTG, 3% elvitegravir). DRV/r with an INSTI was non-inferior to standard of care at Week 48 (HIV viral load  $\geq 50$  copies/mL in 5% for DRV/r with an INSTI vs. 7.6% in the standard-of-care arm; difference  $-2.5\%$  [95% CI,  $-7.6\%$  and  $2.5\%$ ]). Secondary analyses comparing DRV/r with an INSTI versus standard of care revealed decreases in CD4 counts ( $-48.3$  cells/mm<sup>3</sup> [95% CI,  $-93.4$  and  $-3.2$ ;  $P = 0.036$ ] and mean high-density lipoprotein change from baseline ( $-4.1$  mg/dL [95% CI,  $-6.7$  and  $-1.4$ ;  $P = 0.003$ ]), and increases in weight and BMI ( $+1.97$  kg [95% CI,  $1.1$  and  $2.9$ ;  $P < 0.001$ ] and  $+0.66$  kg/m<sup>2</sup> [95% CI,  $0.3$  and  $1.0$ ;  $P < 0.001$ ], respectively). A nested PK substudy in 153 adolescents aged  $\geq 12$  years to <18 years from SMILE also demonstrated that total and unbound DTG concentrations were adequate and well above the protein-adjusted 90% inhibitory concentration for DTG.<sup>54</sup> DTG trough concentrations were also comparable to those measured in adults receiving 50 mg once daily. Apparent clearance of the unbound drug was influenced by total bilirubin concentrations and Asian ethnicity.

## Crushing Film-Coated Tablets for Administration

Dispersible tablets are now considered the preferred formulation for pediatric patients weighing <20 kg, and film-coated tablets should not be used in children weighing <14 kg. In patients who have difficulty swallowing whole tablets and in children weighing >14 kg, when the preferred dispersible tablets are not available, the 10-mg and 50-mg tablets either may be split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which must be consumed **immediately**.<sup>1</sup> In healthy adults, the use of crushed tablets resulted in slightly higher exposures than the use of whole tablets.<sup>55</sup> No information exists on the impact of splitting or crushing film-coated tablets on palatability. Some case reports describe DTG-containing film-coated tablets being crushed and successfully administered via orogastric tube<sup>56</sup> or nasogastric tube.<sup>57</sup> If DTG is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.

## Elvitegravir (EVG)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Tablet: Elvitegravir is available only in fixed-dose combination (FDC) tablets.</p> <p><b>FDC Tablets</b></p> <ul style="list-style-type: none"> <li>[Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> <li>[Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> </ul> <p>When using FDC tablets, refer to other sections of the <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.</a></p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>[Genvoya]</b> Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/c/FTC/TAF)</p> <p><i>Child (Weighing <math>\geq 14</math> to <math>&lt; 25</math> kg)</i></p> <ul style="list-style-type: none"> <li>Limited data are available on the dose of Genvoya in children with weight <math>\geq 14</math> kg to <math>&lt; 25</math> kg. A study is being conducted to assess the safety and efficacy of an investigational low-dose tablet with EVG 90 mg/cobicistat (COBI) 90 mg/FTC 120 mg/TAF 6 mg.</li> </ul> <p><i>Child and Adolescent (Weighing <math>\geq 25</math> kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with food in antiretroviral therapy (ART)–naive or treatment-experienced patients who have been virologically suppressed (HIV RNA <math>&lt; 50</math> copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.</li> </ul> <p><b>[Stribild]</b> Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/c/FTC/TDF)</p> <p><i>Child and Adolescent (Weighing <math>\geq 35</math> kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with food in ART-naive or treatment-experienced patients who have been virologically suppressed (HIV RNA <math>&lt; 50</math> copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.</li> </ul>	<p><b>Genvoya- and Stribild-Associated Adverse Events</b></p> <ul style="list-style-type: none"> <li>Nausea</li> <li>Diarrhea</li> <li>Fatigue</li> <li>Headache</li> </ul> <p><i>TAF-Specific Adverse Events</i></p> <ul style="list-style-type: none"> <li>Increased levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol</li> <li>Glomerular and proximal renal tubular dysfunction (less common when compared to TDF)</li> </ul> <p><i>TDF-Specific Adverse Events</i></p> <ul style="list-style-type: none"> <li>Glomerular and proximal renal tubular dysfunction</li> <li>Decreased bone mineral density</li> <li>Flatulence</li> </ul> <p><i>COBI-Specific Adverse Events</i></p> <ul style="list-style-type: none"> <li>Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine</li> </ul>

	<div data-bbox="805 191 1427 258" data-label="Section-Header"> <h3 style="text-align: center;">Special Instructions</h3> </div> <div data-bbox="805 258 1427 957" data-label="List-Group"> <ul style="list-style-type: none"> <li>• Administer both Genvoya and Stribild with food.</li> <li>• Genvoya and Stribild should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.</li> <li>• When using Genvoya or Stribild, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels &gt;0.4 mg/dL should be closely monitored for renal safety.</li> <li>• Screen patients for hepatitis B virus (HBV) infection before initiating FTC, TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued. In patients with HBV, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF.</li> <li>• For information on crushing and cutting tablets, see the <a href="#">Information on Crushing and Liquid Drug Formulations table</a> from Toronto General Hospital.</li> </ul> </div> <div data-bbox="805 957 1427 1024" data-label="Section-Header"> <h3 style="text-align: center;">Metabolism/Elimination</h3> </div> <div data-bbox="805 1024 1427 1276" data-label="List-Group"> <ul style="list-style-type: none"> <li>• EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.</li> <li>• EVG is available only in combination with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the <a href="#">COBI</a>, <a href="#">TDF</a>, and <a href="#">TAF</a> sections for further details on the metabolism of these drugs.</li> </ul> </div> <div data-bbox="805 1276 1427 1323" data-label="Section-Header"> <h4>EVG Dosing in Patients with Hepatic Impairment</h4> </div> <div data-bbox="805 1323 1427 1396" data-label="List-Group"> <ul style="list-style-type: none"> <li>• Stribild and Genvoya <b>should not be used</b> in patients with severe hepatic impairment.</li> </ul> </div> <div data-bbox="805 1396 1427 1442" data-label="Section-Header"> <h4>EVG Dosing in Patients with Renal Impairment</h4> </div> <div data-bbox="805 1442 1427 1740" data-label="List-Group"> <ul style="list-style-type: none"> <li>• Stribild <b>should not be initiated</b> in patients with estimated CrCl &lt;70 mL/min, and it should be discontinued in patients with estimated CrCl &lt;50 mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.</li> <li>• Genvoya is <b>not recommended</b> in patients with estimated CrCl 15 to &lt;30 mL/min or in patients with estimated CrCl &lt;15 mL/min who are not receiving chronic hemodialysis.</li> </ul> </div>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Absorption:* Elvitegravir (EVG) plasma concentrations are lower with concurrent administration of divalent cations due to the formation of complexes in the gastrointestinal tract and not due to changes in gastric pH. Therefore, Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.<sup>1</sup>
- *Metabolism:* Stribild and Genvoya contain EVG and cobicistat (COBI). COBI itself does not have antiretroviral (ARV) activity, but it is a cytochrome P450 (CYP) 3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir (RTV).<sup>2</sup> EVG is metabolized predominantly by CYP3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative metabolism pathways. EVG is a moderate inducer of CYP2C9. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. In addition, COBI inhibits the adenosine triphosphate–dependent transporters, P-glycoprotein and the breast cancer resistance protein, and the organic anion-transporting (OAT) polypeptides OATP1B1 and OATP1B3. See the [Cobicistat](#) section for a more detailed summary of drug interactions. Multiple drug interactions are possible when using both EVG and COBI. Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain RTV because of the similar effects of COBI and RTV on CYP3A4 metabolism. Coadministration of medications that induce or inhibit CYP3A4 may respectively decrease or increase exposures of EVG and COBI. Coadministration of medications that are CYP3A4 substrates may result in clinically significant adverse reactions that are severe, life-threatening, or fatal, or may result in loss of therapeutic effect if dependent on conversion to an active metabolite due to CYP3A4 inhibition by COBI.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir, in the form of tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Genvoya or Stribild. COBI inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL from baseline in adults. Creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, but the actual GFR might be only minimally changed.<sup>3</sup> Significant increases in serum creatinine levels >0.4 mg/dL from baseline may represent renal toxicity and should be evaluated. People who experience a confirmed increase in serum creatinine levels should be closely monitored for renal toxicity; clinicians should monitor creatinine levels for further increases and perform a urinalysis to look for evidence of proteinuria or glycosuria.<sup>4</sup>

## Major Toxicities

- *More common:* Nausea, diarrhea, fatigue, headache, flatulence
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and FTC. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children who were taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TAF or TDF,



including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TAF or TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Genvoya or Stribild. This nephrotoxicity may be more pronounced in patients with preexisting renal disease.<sup>4</sup> Although postmarketing cases of renal impairment have been reported with TAF, Genvoya, which contains TAF, has an improved bone and renal safety profile in children and adults when compared to Stribild, which contains TDF.<sup>5,6</sup> However, Genvoya is associated with greater increases in lipid levels than Stribild, according to findings from large-scale clinical trials in adults.

## 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. There is phenotypic cross-resistance between EVG and raltegravir (RAL).<sup>7</sup>

## Pediatric Use

### *Approval*

Genvoya (EVG/c/FTC/TAF) is approved by the U.S. Food and Drug Administration (FDA) for use in ARV-naïve children and adolescents with HIV weighing  $\geq 25$  kg. It also can be used to replace the current ARV regimen in those 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 mutations associated with resistance to the individual components of Genvoya.

Stribild (EVG/c/FTC/TDF) is approved by the FDA as a complete regimen for use in children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg. It can also be used to replace the current ARV regimen in those 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 mutations associated with resistance to the individual components of Stribild.<sup>8</sup>

### *Efficacy*

EVG/c/FTC/TDF was found to be non-inferior to efavirenz/emtricitabine/TDF (EFV/FTC/TDF)<sup>9-11</sup> and atazanavir/ritonavir plus FTC/TDF in adults through 144 weeks of treatment.<sup>12-14</sup>

Studies of EVG/c/FTC/TDF and EVG/c/FTC/TAF in children with HIV aged  $\geq 12$  years and weighing  $\geq 35$  kg have demonstrated **90% efficacy (as measured by virological suppression)** similar to that seen in adults through 24 weeks and 48 weeks of study, respectively.<sup>15,16</sup>

EVG/c/FTC/TAF is FDA approved to treat children weighing  $\geq 25$  kg based on 24 weeks of data in 23 children.<sup>17</sup> In this study, **all** children who had been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months were switched from their current regimens to EVG/c/FTC/TAF **and all participants maintained virological suppression (HIV-1 RNA  $< 50$  copies/mL) at Week 24.**

A retrospective analysis of integrase strand transfer inhibitor (INSTI) use in children and adolescents showed that 83.7% (61/73) of patients on an **elvitegravir/cobicistat** (EVG/c)-containing therapy

continued their prescribed regimen through the end of the study follow-up period (median [interquartile range (IQR)] 2.0 [1.4–2.7] years of exposure). Treatment interruption due to virologic occurred in 4.1% (3/73) of those on EVG/c, which was comparable to that of dolutegravir (DTG)-based regimens (3.7% [5 of 134 participants]) and lower than RAL-based regimens (17.3% [19 of 110 participants]). Two of the participants who experienced virologic failures with EVG had major INSTI drug-resistance mutations, but both attained virologic suppression after switching to regimens containing darunavir (DRV) or DRV with DTG.<sup>18</sup>

In a PK, safety, and efficacy study with a low-dose tablet in children aged  $\geq 2$  years and weighing  $\geq 14$  kg to  $< 25$  kg, children had to be virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months prior to entry.<sup>19</sup> In the most recent analysis, virologic suppression was maintained<sup>20</sup> in 27 (100%) of 27 children at Week 16, 26 (96%) of 27 children at Week 24, and 26 (96%) of 27 children at Week 48. No participant discontinued the study drug because of adverse events or met the criteria for resistance analyses through Week 48. At least 90% of children reported that swallowing the low-dose tablet was “easy” or “super easy” and perceived the tablet size when swallowing as “okay” at baseline, Week 4, and Week 24.<sup>19</sup>

## ***Pharmacokinetics***

### **EVG/c/FTC/TDF (Stribild)**

The PK of EVG 150 mg/c 150 mg/FTC 200 mg/TDF 300 mg tablet were evaluated in 14 treatment-naive adolescents with HIV who were between 12 and  $< 18$  years of age and weighing  $\geq 35$  kg. EVG area under the plasma concentration versus time curve over the dosing interval ( $AUC_{\tau}$ ) and peak concentrations ( $C_{\max}$ ) were 30% higher (90% confidence interval [CI], 105% to 162%) and 42% higher (90% CI, 116% to 173%), respectively, in comparison to historical data in adults. EVG concentrations at the end of the dosing interval ( $C_{\tau}$ ) were 6% higher (90% CI, 70% to 160%) than in adults, and approximately ninefold higher than the protein-adjusted 95% inhibitory concentration (PA-IC<sub>95</sub>) of 44.5 ng/mL for EVG. COBI, FTC, and TFV exposures were comparable to those measured in adults.<sup>16</sup>

### **EVG/c/FTC/TAF (Genvoya)**

The PK of EVG 150 mg/c 150 mg/FTC 200 mg/TAF 10 mg tablet have been evaluated in adolescents 12 to  $< 18$  years of age weighing  $\geq 35$  kg and children 6 to  $< 12$  years of age weighing  $\geq 25$  kg.<sup>17</sup>  $AUC_{\tau}$ ,  $C_{\max}$ , and  $C_{\tau}$  for EVG, COBI, FTC, TAF, and TFV were comparable to or higher than those measured in adults with HIV in both cohorts (see Tables A and B below).

The PK of a low-dose FDC tablet containing EVG 90 mg/c 90 mg/FTC 120 mg/TAF 6 mg were evaluated in 27 children with HIV weighing  $\geq 14$  kg and  $< 25$  kg.<sup>19</sup> EVG and TAF  $AUC_{\tau}$  were higher in comparison to historical data in adults receiving full-strength Genvoya (see Tables A and B below). EVG  $C_{\tau}$  was 21% lower (90% CI [53.1% to 117%]) in children versus adults but was approximately 4.4-fold higher and ninefold higher than the PA-IC<sub>95</sub> and protein-adjusted 50% inhibitory concentration (PA-IC<sub>50</sub>) for wild-type virus, respectively. However, EVG  $C_{\tau}$  measured in this cohort was lower than those previously measured in children and adolescents weighing  $\geq 25$  kg on EVG at the 150-mg dose. COBI, FTC, and TFV exposures were all comparable to or higher than historical data in adults.

**Table A. Pharmacokinetics of EVG, COBI, FTC, TAF, and TFV (Genvoya) in Children and Adolescents with HIV Between 2 to <18 Years of Age and Weighing ≥14 kg**

Component	Parameter	Children Aged ≥2 Years and Weighing ≥14 to <25 kg <sup>19</sup>		Children Aged 6 to <12 Years and Weighing ≥25 kg <sup>17</sup>		Adolescents Aged 12 to <18 Years and Weighing ≥35 kg <sup>15</sup>		Adults <sup>a15,17</sup>	
		n	GLSM	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
EVG	AUC <sub>1au</sub> (ng·h/mL)	27	29,900	22	33,814 (58%)	24	23,840 (26%)	19	22,800 (35%)
	C <sub>max</sub> (ng/mL)	27	2,850	23	3,055 (39%)	24	2,230 (19%)	19	2,100 (34%)
	C <sub>1au</sub> (ng/mL)	27	195	23	370 (119%)	24	301 (81%)	19	290 (62%)
COBI	AUC <sub>1au</sub> (ng·h/mL)	27	12,300	20	15,891 (52%)	23	8,241 (36%)	19	9,500 (34%)
	C <sub>max</sub> (ng/mL)	27	1,270	23	2,079 (47%)	24	1,202 (35%)	19	1,500 (28%)
	C <sub>1au</sub> (ng/mL)	27	16.6	23	96 (169%)	15	25 (180%)	19	20 (85%)
FTC	AUC <sub>1au</sub> (ng·h/mL)	27	18,600	22	20,629 (19%)	24	14,424 (24%)	19	11,714 (17%)
	C <sub>max</sub> (ng/mL)	27	2,810	23	3,397 (27%)	24	2,265 (23%)	19	2,056 (20%)
	C <sub>1au</sub> (ng/mL)	27	77.4	23	115 (24%)	23	102 (39%)	19	95 (47%)
TAF	AUC <sub>1au</sub> (ng·h/mL)	27	344	23	333 (45%)	24	189 (56%)	539	206 (72%)
	C <sub>max</sub> (ng/mL)	27	218	23	313 (61%)	24	167 (64%)	539	162 (51%)
TFV	AUC <sub>1au</sub> (ng·h/mL)	27	327	23	440 (21%)	23	288 (19%)	841	293 (27%)
	C <sub>max</sub> (ng/mL)	27	19.1	23	26 (21%)	23	18 (24%)	841	15 (26%)
	C <sub>1au</sub> (ng/mL)	27	11.1	23	15 (25%)	23	10 (21%)	841	11 (29%)
TFV-DP in PBMC	C <sub>0h</sub> (fmol/10 <sup>6</sup> cells)	—	—	—	—	12	222 (94%)	21	121 (91%)

<sup>a</sup> Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from a Phase 2 study GS 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 GS studies 104 and 111.

**Key:** AUC<sub>1au</sub> = area under the plasma concentration versus time curve over the dosing interval; C<sub>0h</sub> = concentration at time 0 (pre-dose); C<sub>max</sub> = maximum observed plasma concentration of drug; C<sub>1au</sub> = observed drug concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; EVG = elvitegravir; fmol = femtomole; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; ng = nanogram; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir-diphosphate

**Table B. Comparisons of EVG, COBI, FTC, TAF, and TFV (Genvoya) Pharmacokinetics in Children and Adolescents with HIV Between 2 and <18 Years of Age and Weighing ≥14 kg to Adult Values**

Component	Parameter	% GLSM (90% CI) Compared with Adult Values <sup>a</sup>			
		Dose (mg)	Children Aged ≥2 Years and Weighing ≥14 to <25 kg <sup>17</sup>	Dose (mg)	Children Aged 6 to <12 Years and Weighing ≥25 kg <sup>19</sup>
EVG	AUC <sub>1au</sub> (ng·h/mL)	90	139 (112,172)	150	134 (104,173)
	C <sub>max</sub> (ng/mL)		143 (113,180)		141 (115,173)
	C <sub>1au</sub> (ng/mL)		79 (53,117)		86 (55,133)
COBI	AUC <sub>1au</sub> (ng·h/mL)	90	—	150	158 (126,198)
	C <sub>max</sub> (ng/mL)		—		127 (98,165)
	C <sub>1au</sub> (ng/mL)		—		171 (95,310)
FTC	AUC <sub>1au</sub> (ng·h/mL)	120	—	200	175 (160,192)
	C <sub>max</sub> (ng/mL)		—		164 (145,184)
	C <sub>1au</sub> (ng/mL)		—		125 (107,146)
TAF	AUC <sub>1au</sub> (ng·h/mL)	6	193 (166,224)	10	171 (147,199)
	C <sub>max</sub> (ng/mL)		150 (116,195)		182 (146,225)
TFV	AUC <sub>1au</sub> (ng·h/mL)	6	—	10	152 (142,163)
	C <sub>max</sub> (ng/mL)		—		173 (161,186)
	C <sub>1au</sub> (ng/mL)		—		143 (132,155)

<sup>a</sup> Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

**Key:** AUC<sub>1au</sub> = area under the plasma concentration versus time curve over the dosing interval; C<sub>max</sub> = maximum observed plasma concentration of drug; COBI = cobicistat; C<sub>1au</sub> = observed drug concentration at the end of the dosing interval; CI = confidence interval; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; mg = milligram; ng = nanogram; TAF = tenofovir alafenamide; TFV = tenofovir

### ***Coadministration of Elvitegravir, Cobicistat, and Darunavir***

The combination of Stribild or Genvoya plus DRV may provide a low-pill-burden regimen for **treatment**-experienced individuals. However, an unfavorable drug interaction between EVG/c and DRV is possible, and the available data on the **significance** of the interaction **and efficacy** are conflicting.<sup>21-24</sup> The most rigorous drug interaction study in HIV-seronegative adults found 21% lower DRV trough concentrations (C<sub>trough</sub>) and 52% lower EVG C<sub>trough</sub> **in combination** with DRV 800 mg plus EVG/c 150 mg/150 mg once daily compared to the administration of either **DRV/c** 800 mg/150 mg once daily or EVG/c 150 mg/150 mg once daily alone.<sup>25</sup> Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults who were on five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus DRV 800 mg once daily.<sup>23</sup> Given

the uncertainty around the true magnitude of the drug interaction and the absence of **pediatric** data, viral load should be closely monitored in children taking this combination.

## **Toxicity**

In studies comparing EVG/c/FTC/TDF or EVG/c/FTC/TAF over 48 weeks in 1,733 adults, those receiving EVG/c/FTC/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL;  $P < 0.0001$ ), significantly less proteinuria (median percent change in protein  $-3\%$  vs.  $+20\%$ ;  $P < 0.0001$ ), and a significantly smaller decrease in BMD at the spine (mean percent change  $-1.30\%$  vs.  $-2.86\%$ ;  $P < 0.0001$ ) and hip ( $-0.66\%$  vs.  $-2.95\%$ ;  $P < 0.0001$ ).<sup>6</sup> Larger increases in fasting lipid levels were observed with EVG/c/FTC/TAF than with EVG/c/FTC/TDF; the median increases in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were all higher in patients who received EVG/c/FTC/TAF.

**In children and adolescents, EVG/c/FTC/TAF is generally preferred over EVG/c/FTC/TDF because of the lower risk of renal and bone toxicity with EVG/c/FTC/TAF compared to EVG/c/FTC/TDF (see the [Tenofovir Alafenamide](#) section).** Long-term bone safety data through 96 weeks with EVG/c/FTC/TAF in adolescents weighing  $\geq 35$  kg revealed no concerns for toxicity<sup>26</sup> in this age group on the basis of BMD (median change from baseline spine BMD height-age [HA] z-score  $+0.14$  and total body less head [TBLH] HA z-score of  $-0.07$ ) and serum biomarkers of bone formation and resorption.<sup>27</sup>

In the approval study of EVG/c/FTC/TAF in children weighing  $\geq 25$  kg, no study discontinuations occurred due to medication toxicity. Long-term bone safety data with EVG/c/FTC/TAF through 96 weeks revealed no concerns for toxicity in this cohort on the basis of BMD (median change from baseline spine BMD HA z-score of  $-0.2$  and TBLH HA z-score of  $-0.32$ ) and serum biomarkers of bone formation and resorption.<sup>20</sup> A concerning decline in CD4 T lymphocyte (CD4) cell counts was observed in all 23 children over the first 24 weeks of EVG/c/FTC/TAF treatment.<sup>17</sup> CD4 counts declined by a median of 130 cells/mm<sup>3</sup> (with a range of  $-472$  cells/mm<sup>3</sup> to 266 cells/mm<sup>3</sup>) from baseline. However, after enrolling additional children (for a total of 52 participants),<sup>28</sup> the median CD4 count decline at 48 weeks was 25 cells/mm<sup>3</sup> and at 96 weeks was 45 cells/mm<sup>3</sup>. Additionally, the CD4 percentage did not significantly change across Weeks 24, 48, and 96.<sup>20</sup> The mechanism for the reduction in CD4 count is unclear, and this reduction has only been reported in this study. Plasma exposures of all four drugs were higher in these children than the plasma exposures seen in historical data from adults, but no association was identified between plasma exposures of the four components of EVG/c/FTC/TAF and CD4 counts.<sup>29</sup>

In an ongoing PK, safety, and efficacy study with a low-dose EVG/c/FTC/TAF tablet in children aged  $\geq 2$  years and weighing  $\geq 14$  kg to  $< 25$  kg,<sup>19</sup> long-term bone safety data with the low-dose formulation through 48 weeks revealed no concerns for bone safety in this cohort on the basis of BMD (median change from baseline in spine BMD HA z-score  $+0.14$  and TBLH HA z-score of  $-0.06$ ) and serum biomarkers of bone formation and resorption.<sup>27</sup> CD4 counts decreased<sup>20</sup> by a mean of 187 cells/mm<sup>3</sup> between baseline and Week 48, although the CD4 percentage did not differ (mean [standard deviation] change of 0.0 [ $< 5.0$ ]). **In a cumulative analysis of two pediatric cohorts (Cohort 2 aged 6 to  $< 12$  years and weighing  $\geq 25$  kg and Cohort 3 aged  $\geq 2$  years and weighing  $\geq 14$  kg to  $< 25$  kg) on EVG/c/FTC/TAF once daily for at least 48 weeks, the absolute lymphocyte counts and absolute CD4 counts decreased from baseline to Week 48 in both cohorts, with larger decreases in the younger cohort.<sup>30</sup> Median (IQR) absolute lymphocyte counts ( $\times 10^3$  per  $\mu\text{L}$ ) at baseline in Cohort 2**

and Cohort 3 were 2.31 (range, 1.92–2.78) and 2.96 (range, 2.39–3.82), respectively. The absolute lymphocyte counts decreased during treatment (particularly in Cohort 3), with changes of  $-0.04$  (range,  $-0.67$  to  $0.29$ ) and  $-0.52$  (range,  $-1.16$  to  $0.05$ ) in Cohorts 2 and 3, respectively, at Week 48. Small decreases were seen in median (IQR) absolute CD4 counts (cells/ $\mu$ L), with changes of  $-33$  ( $-194$  to  $80$ ) and  $-187$  ( $-370$  to  $44$ ) in Cohorts 2 and 3, respectively, at Week 48. However, the relative proportion of CD4 cells and the CD4:CD8 ratio remained stable during treatment. Overall, the decline in absolute CD4 counts mirrored known physiological fluctuations in young children and was mainly observed in those aged  $<6$  years.<sup>30</sup>

## Raltegravir (RAL, Isentress)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations																			
<p>Tablet: 400 mg (film-coated poloxamer tablet)</p> <p>High-Dose (HD) Tablet: 600 mg (film-coated poloxamer tablet)</p> <p>Chewable Tablets: 100 mg (scored) and 25 mg</p> <p>Granules for Oral Suspension: Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for a final concentration of 10 mg/mL</p> <p><i>Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.</i></p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>																			
Dosing Recommendations	Selected Adverse Events																		
<p><b>Note:</b> No dosing information is available for preterm infants or infants weighing &lt;2 kg at birth. See <a href="#">Table 13. Antiretroviral Drug Dosing Recommendations for Newborns</a> for information about using raltegravir (RAL) for the prevention of perinatal HIV transmission.</p> <p><b>Neonate (Weighing ≥2 kg) Dose<sup>a,b</sup></b></p> <p><b>RAL Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks</b></p> <p><i>Neonates Aged ≥37 Weeks and Weighing ≥2 kg</i></p> <table border="1"> <thead> <tr> <th>Weight</th> <th>Volume (Dose) of Suspension<sup>b</sup></th> </tr> </thead> <tbody> <tr> <td><b>Birth to 1 Week of Age: Once-Daily Dosing</b></td> <td><b>Approximately 1.5 mg/kg per Dose</b></td> </tr> <tr> <td>2 kg to &lt;3 kg</td> <td>0.4 mL (4 mg) once daily</td> </tr> <tr> <td>3 kg to &lt;4 kg</td> <td>0.5 mL (5 mg) once daily</td> </tr> <tr> <td>4 kg to &lt;5 kg</td> <td>0.7 mL (7 mg) once daily</td> </tr> <tr> <td><b>1–4 Weeks of Age: Twice-Daily Dosing</b></td> <td><b>Approximately 3 mg/kg per Dose</b></td> </tr> <tr> <td>2 kg to &lt;3 kg</td> <td>0.8 mL (8 mg) twice daily</td> </tr> <tr> <td>3 kg to &lt;4 kg</td> <td>1 mL (10 mg) twice daily</td> </tr> <tr> <td>4 kg to &lt;5 kg</td> <td>1.5 mL (15 mg) twice daily</td> </tr> </tbody> </table>	Weight	Volume (Dose) of Suspension <sup>b</sup>	<b>Birth to 1 Week of Age: Once-Daily Dosing</b>	<b>Approximately 1.5 mg/kg per Dose</b>	2 kg to <3 kg	0.4 mL (4 mg) once daily	3 kg to <4 kg	0.5 mL (5 mg) once daily	4 kg to <5 kg	0.7 mL (7 mg) once daily	<b>1–4 Weeks of Age: Twice-Daily Dosing</b>	<b>Approximately 3 mg/kg per Dose</b>	2 kg to <3 kg	0.8 mL (8 mg) twice daily	3 kg to <4 kg	1 mL (10 mg) twice daily	4 kg to <5 kg	1.5 mL (15 mg) twice daily	<ul style="list-style-type: none"> <li>Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis</li> <li>Nausea, diarrhea</li> <li>Headache, dizziness, fatigue</li> <li>Insomnia</li> <li>Fever</li> <li>Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis</li> </ul>
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	Special Instructions																		
	<ul style="list-style-type: none"> <li>RAL can be given without regard to food.</li> <li>Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids <b>is not recommended</b> with any RAL formulations.</li> <li>Significant drug interactions are more likely to occur when the RAL HD formulation is used once daily. <b>The following drugs should not be coadministered with once-daily RAL HD dosing:</b> calcium carbonate antacids, rifampin, tipranavir/ritonavir, and etravirine.</li> <li>Chewable tablets can be chewed, crushed (before administration), or swallowed whole.</li> <li>Film-coated tablets, including HD tablets, must be swallowed whole.</li> </ul>																		



<sup>a</sup> RAL is metabolized by uridine diphosphate glucuronyl transferase (UGT) 1A1, and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4 to 6 weeks of life.

<sup>b</sup> For neonates, most of the prepared oral suspension will be discarded. The volume for the required dose is much smaller than the 10 mL suspension that is prepared.

**Note:** If the birthing parent has taken RAL 2 to 24 hours prior to delivery, the neonate's first dose **may** be delayed until 24 to 48 hours after birth.

**Infant >4 Weeks of Age and Child (Weighing ≥3 kg to <20 kg) Dose**

- For children weighing 3 to 20 kg, either oral suspension or chewable tablets can be used.

**RAL Oral Suspension Dosing Table for Patients Aged >4 Weeks<sup>a</sup>**

**Note:** The maximum dose of oral suspension is 10 mL (RAL 100 mg) twice daily.

Weight	Twice-Daily Volume (Dose) of Suspension <sup>b</sup>
3 kg to <4 kg	2.5 mL (25 mg) twice daily
4 kg to <6 kg	3 mL (30 mg) twice daily
6 kg to <8 kg	4 mL (40 mg) twice daily
8 kg to <10 kg	6 mL (60 mg) twice daily
10 kg to <14 kg	8 mL (80 mg) twice daily
14 kg to <20 kg	10 mL (100 mg) twice daily

<sup>a</sup> The weight-based dose recommendation for the oral suspension is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

<sup>b</sup> For neonates, most of the prepared oral suspension will be discarded, because the volume for the required dose is much smaller than 10 mL.

**Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets**

*Children Weighing ≥3 kg*

- Weighing <25 kg
  - Chewable tablets twice daily. See the table below for chewable tablet doses.
- Weighing ≥25 kg
  - RAL 400-mg, film-coated tablets twice daily **or** chewable tablets twice daily. See the table below for chewable tablet doses.

- The chewable tablets and oral suspension have better bioavailability than the film-coated tablets. Because the formulations are not interchangeable, **do not substitute** chewable tablets or oral suspension for film-coated tablets. See specific recommendations for proper dosing of different formulations.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.

- **Instructions for preparing and administering the chewable tablet as a crushed tablet are as follows:** Place the tablet(s) in a small, clean cup. For each tablet, add a teaspoon (~5 mL) of liquid (e.g., water, juice, or breast milk). Within 2 minutes, the tablet(s) will absorb the liquid and fall apart. Using a spoon, crush any remaining pieces of the tablet(s). Immediately administer the entire dose orally. If any portion of the dose is left in the cup, add another teaspoon (~5 mL) of liquid, swirl, and administer immediately.

- The chewable tablets contain phenylalanine, a component of aspartame. Phenylalanine can be harmful to patients with phenylketonuria, and the necessary dietary adjustments should be made in consultation with a metabolic specialist.

- The oral suspension comes in a kit that includes instructions for use, mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document.<sup>1</sup> Each single-use foil packet contains 100 mg of RAL, which will be suspended in 10 mL of water for a final concentration of RAL 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.

- **Do not shake the oral suspension.** Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document. For neonates, most of the prepared oral suspension will be discarded, because the volume for the required dose is much smaller than 10 mL.

**Metabolism/Elimination**

- UGT1A1-mediated glucuronidation

**RAL Dosing in Patients with Hepatic Impairment**

- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving RAL twice daily.

<p><i>Children and Adolescents Weighing <math>\geq 40</math> kg</i></p> <ul style="list-style-type: none"> <li>• Two RAL 600-mg HD tablets (1,200 mg) once daily</li> <li>• This dose is for antiretroviral therapy-naïve or virologically suppressed patients who are on an initial dose of RAL 400 mg twice daily.</li> </ul> <p><b>Chewable Tablet Dosing Table<sup>a</sup></b></p> <p><b>Note:</b> The maximum dose of chewable tablets is RAL 300 mg twice daily.</p> <table border="1"> <thead> <tr> <th>Weight</th> <th>Twice-Daily Dose</th> <th>Number of Chewable Tablets</th> </tr> </thead> <tbody> <tr> <td>3 kg to &lt;6 kg</td> <td>RAL 25 mg</td> <td>1 tablet (25 mg)</td> </tr> <tr> <td>6 kg to &lt;10 kg</td> <td>RAL 50 mg</td> <td>2 tablets (25 mg)</td> </tr> <tr> <td>10 kg to &lt;14 kg</td> <td>RAL 75 mg</td> <td>3 tablets (25 mg)</td> </tr> <tr> <td>14 kg to &lt;20 kg</td> <td>RAL 100 mg</td> <td>1 tablet (100 mg)</td> </tr> <tr> <td>20 kg to &lt;28 kg</td> <td>RAL 150 mg</td> <td>1½ tablets<sup>b</sup> (100 mg)</td> </tr> <tr> <td>28 kg to &lt;40 kg</td> <td>RAL 200 mg</td> <td>2 tablets (100 mg)</td> </tr> <tr> <td><math>\geq 40</math> kg</td> <td>RAL 300 mg</td> <td>3 tablets (100 mg)</td> </tr> </tbody> </table> <p><sup>a</sup> The weight-based dose recommendation for the chewable tablet is based on a dose of approximately RAL 6 mg/kg per dose twice daily.</p> <p><sup>b</sup> The RAL 100-mg chewable tablet can be divided into equal halves.</p>	Weight	Twice-Daily Dose	Number of Chewable Tablets	3 kg to <6 kg	RAL 25 mg	1 tablet (25 mg)	6 kg to <10 kg	RAL 50 mg	2 tablets (25 mg)	10 kg to <14 kg	RAL 75 mg	3 tablets (25 mg)	14 kg to <20 kg	RAL 100 mg	1 tablet (100 mg)	20 kg to <28 kg	RAL 150 mg	1½ tablets <sup>b</sup> (100 mg)	28 kg to <40 kg	RAL 200 mg	2 tablets (100 mg)	$\geq 40$ kg	RAL 300 mg	3 tablets (100 mg)	<ul style="list-style-type: none"> <li>• No studies have been conducted on the use of RAL HD in patients with hepatic impairment. Therefore, administering RAL HD is <b>not recommended</b> in patients with hepatic impairment.</li> <li>• The effect of severe hepatic impairment on RAL pharmacokinetics has not been studied.</li> </ul> <p><b>RAL Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• No dose adjustment is necessary in patients with any degree of renal impairment.</li> </ul>
Weight	Twice-Daily Dose	Number of Chewable Tablets																							
3 kg to <6 kg	RAL 25 mg	1 tablet (25 mg)																							
6 kg to <10 kg	RAL 50 mg	2 tablets (25 mg)																							
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- **Metabolism:** The major route of raltegravir (RAL) elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT) 1A1.
- Coadministering RAL with inducers of UGT1A1—such as rifampin and tipranavir—may result in reduced plasma concentrations of RAL. Inhibitors of UGT1A1—such as atazanavir— may increase plasma concentrations of RAL. No dosing modifications are recommended when RAL is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, RAL high-dose (HD) tablets **should not be coadministered** with TPV/r.
- In adults, an increased dose of RAL is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended RAL dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily RAL HD tablets. In children aged 4 weeks to <12 years who had tuberculosis (TB)/HIV coinfection and were taking rifampin, RAL 12 mg/kg per dose twice daily of the chewable tablet formulation safely achieved pharmacokinetic (PK) targets.<sup>2,3</sup> In a single case report of a 6-month-old infant receiving RAL oral granules for suspension and

rifampicin for TB prophylaxis, three to four times the currently recommended dose of 12 mg/kg twice daily was needed<sup>4</sup> to achieve target trough concentrations ( $C_{\text{trough}}$ ) >0.022 mg/L.

- Aluminum-containing antacids and magnesium-containing antacids may reduce RAL plasma concentrations and **should not be coadministered** with RAL.
- Significant drug interactions may be more likely to occur with RAL HD once daily.  $C_{\text{trough}}$  in adults is approximately 30% lower with RAL HD 1,200 mg once daily than with RAL 400 mg twice daily. A lower  $C_{\text{trough}}$  increases the potential for clinically significant drug interactions with interfering drugs that decrease RAL exposure and further lower  $C_{\text{trough}}$ . In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the RAL HD formulation: calcium carbonate antacids, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on RAL is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.
- Before administering RAL, clinicians should carefully review a patient's medication profile for potential drug interactions with RAL.

## Major Toxicities

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, itching, insomnia.
- *Less common:* Abdominal pain, vomiting. Patients with chronic active hepatitis B virus infection and/or hepatitis C virus infection are more likely to experience a worsening adverse events (AEs) grade from baseline for laboratory abnormalities of aspartate aminotransferase, alanine aminotransferase, or total bilirubin than patients who are not coinfecting.
- *Rare:* Moderate-to-severe increase in creatine phosphokinase levels. Use RAL with caution in patients who are receiving medications that are associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with a history of these conditions. Rash (including Stevens-Johnson syndrome), hypersensitivity reaction, **DRESS (drug reaction with eosinophilia and systemic symptoms)**,<sup>5,6</sup> and toxic epidermal necrolysis. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

## Resistance

The International AIDS Society–USA maintains a [list of updated HIV resistance mutations](#), and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## Pediatric Use

### *Approval*

RAL is an integrase strand transfer inhibitor that is approved by the U.S. Food and Drug Administration (FDA) for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV in pediatric patients weighing  $\geq 2$  kg. The current pediatric FDA approval and dose recommendations are based on evaluations of 122 patients aged  $\geq 4$  weeks to 18 years who participated in [IMPAACT P1066](#) and 42 full-term neonates who were treated for  $\leq 6$  weeks starting from birth and followed for a total of 24 weeks during [IMPAACT P1110](#).<sup>7</sup>

The FDA has approved RAL HD, which allows once-daily dosing, for use in children and adolescents weighing  $\geq 40$  kg.

### ***Efficacy in Clinical Trials***

RAL has been evaluated in adults in three large randomized clinical trials: STARTMRK, SPRING-2, and AIDS Clinical Trials Group (ACTG) A5257. STARTMRK compared the safety and efficacy of a RAL-containing regimen and an efavirenz (EFV)-containing regimen. At 48 weeks, RAL was non-inferior to EFV. However, more patients discontinued EFV during the longer follow-up periods of 4 and 5 years, and RAL was found to be virologically and immunologically superior to EFV.<sup>8-10</sup> Results from the SPRING-2 study in treatment-naive adults showed that RAL and dolutegravir (DTG) were equally effective and had similar safety profiles.<sup>11</sup> ACTG A5257 compared RAL to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but RAL had better tolerability.<sup>12</sup> The ONCEMRK study compared RAL 1,200 mg once daily (taken as two 600-mg RAL HD tablets) to RAL 400 mg twice daily in treatment-naive adults. Once-daily dosing with RAL 1,200 mg (taken as two 600-mg HD tablets) was found to be as effective as dosing with RAL 400 mg twice daily. Discontinuation rates due to AEs were not different between the two groups.<sup>13</sup> Once-daily dosing of RAL using the HD tablets was approved by the FDA for adults and children weighing  $\geq 40$  kg who are either treatment naive or virologically suppressed on a twice-daily RAL regimen.

RAL was studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated PK, safety, tolerability, and efficacy. In 96 participants aged 2 to 18 years who were mostly antiretroviral therapy (ART) experienced, 79.1% of the patients achieved a favorable viral load response (i.e., viral loads  $< 400$  copies/mL or  $\geq 1$  log<sub>10</sub> decline in viral load) while receiving the currently recommended dose of RAL. Infants and toddlers aged  $\geq 4$  weeks to  $< 2$  years also were enrolled in IMPAACT P1066 and received treatment with RAL oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads<sup>14-16</sup>  $< 400$  copies/mL.

A systematic review of observational and clinical trials published on the effectiveness and safety of RAL and DTG for treating children and adolescents with HIV was conducted by the World Health Organization. The authors concluded that both medications are safe and effective as preferred regimens.<sup>17</sup>

### **Efficacy and Pharmacokinetics of Once-Daily Dosing in Children and Adults**

RAL PK exhibit considerable intrasubject and intersubject variability.<sup>18,19</sup> Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive patients with HIV were randomized to receive RAL 800 mg once daily or RAL 400 mg twice daily. After 48 weeks of treatment, the percent of patients who achieved HIV RNA viral loads  $< 50$  copies/mL was 83% in the once-daily group, compared with 89% in the twice-daily group. Patients in the once-daily arm with C<sub>trough</sub> concentrations  $< 45$  nM (20 ng/mL) were at greater risk of experiencing treatment failure.<sup>18,19</sup> Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower C<sub>trough</sub> concentrations suggests that maintaining RAL trough plasma concentrations  $> 45$  nM (20 ng/mL) is important for efficacy.<sup>18,19</sup>

The highest concentration (C<sub>max</sub>) is approximately six times higher in patients receiving RAL 1,200 mg once daily than in those receiving RAL 400 mg twice daily, with a twofold higher area under the curve (AUC). Although modeling and simulations for pediatric patients indicate that PK targets are met using the once-daily RAL 1,200-mg dose, no clinical data exist on the use of this dose

in children weighing <50 kg. Six children in IMPAACT P1066 had drug exposures that were similar to those observed in ONCEMRK, but all six children weighed >50 kg. Dose-related central nervous system toxicities—such as insomnia or hyperactivity—may occur in children who are exposed to very high concentrations of RAL.<sup>7</sup>

## Efficacy and Pharmacokinetics in Children

IMPAACT P1066 evaluated the PK, safety, and efficacy of RAL in treatment-experienced children aged 4 weeks to 18 years. A summary of RAL steady-state PK parameters, following administration of the recommended twice-daily doses (approximately 6 mg/kg twice daily), can be found in Table A below.<sup>15,16</sup>

**Table A. Raltegravir Steady-State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Twice-Daily Doses: IMPAACT P1066**

Body Weight	Formulation	Dose	N <sup>a</sup>	Geometric Mean (% CV) <sup>b</sup> AUC <sub>0–12h</sub> (μM·h) <sup>c,d</sup>	Geometric Mean (% CV) <sup>b</sup> C <sub>12h</sub> (nM) <sup>c,d</sup>
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121%)	233 (157%)
≥25 kg	Chewable tablet	Weight-based dosing <sup>e</sup>	9	22.1 (36%)	113 (80%)
11 kg to <25 kg	Chewable tablet	Weight-based dosing <sup>e</sup>	13	18.6 (68%)	82 (123%)
3 kg to <20 kg	Oral suspension	Weight-based dosing <sup>e</sup>	19	24.5 (43%)	113 (69%)

<sup>a</sup> Number of patients with intensive PK results at the final recommended dose

<sup>b</sup> Geometric coefficient of variation

<sup>c</sup> Pharmacokinetic targets for film-coated tablets and chewable tablets: AUC<sub>0–12h</sub> 14–25 μM·h (6–11 mg·h/L); C<sub>12h</sub> nM ≥33 nM (14.7 ng/mL)

<sup>d</sup> Pharmacokinetic targets for oral suspension: AUC<sub>0–12h</sub> 14–45 μM·h (6–20 mg·h/L); C<sub>12h</sub> nM ≥75 nM (33.3 ng/mL)

<sup>e</sup> To approximate 6 mg/kg twice daily

**Key:** AUC = area under the curve; AUC<sub>0–12h</sub> = AUC from time zero to 12 hours after drug administration; C<sub>12h</sub> = concentration at 12 hours (trough); CV = coefficient of variation

## Children Aged 2 Years to 18 Years

IMPAACT P1066 was a Phase 1/2 open-label, multicenter study that evaluated the PK profile, safety, tolerability, and efficacy of various formulations of RAL in ART-experienced children and adolescents with HIV aged 2 to 18 years. RAL was administered in combination with an optimized background ARV regimen.<sup>16,20</sup> Participants received either the RAL 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing ≥25 kg) or the chewable tablet formulation at a dose of RAL 6 mg/kg twice daily (patients aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included an intensive PK evaluation in various age cohorts (Cohort 1: 12 years to <19 years; Cohort 2: 6 years to <12 years; Cohort 3: 2 years to <6 years). Doses were selected with the aim of achieving target PK parameters that were similar to those seen in adults: PK targets were a geometric mean (GM) AUC from time zero to 12 hours after drug administration (AUC<sub>0–12h</sub>) of 14 μM·h to 25 μM·h and a GM 12-hour concentration (C<sub>12h</sub>) >33 nM. Additional participants were then enrolled in each age cohort to evaluate the long-term efficacy, tolerability, and safety of RAL.



A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of RAL. Only treatment-experienced patients were eligible to enroll, and the optimized regimen was determined by the site investigators. Adolescents tended to be more treatment experienced and have more advanced disease than those in the younger cohorts, with 75% having the Centers for Disease Control and Prevention Category B or C classification of HIV infection. Ninety-six participants completed 48 weeks of treatment. Seventy-nine percent of participants achieved HIV RNA <400 copies/mL, and 57% of participants achieved HIV RNA <50 copies/mL, with a mean CD4 T lymphocyte (CD4) cell count increase<sup>16</sup> of 156 cells/mm<sup>3</sup> (4.6%). Among 36 participants who experienced virologic failure, the development of drug resistance and/or poor adherence were contributing factors. Genotypic resistance data were available for 34 patients who experienced virologic failure, and RAL-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of AEs through Week 48 were comparable to those observed in adult studies. AEs were commonly reported, but few serious AEs were considered to be drug related. Patients with AEs that were considered to be drug related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia, as well as one patient with a Grade 2 allergic rash on Day 17 and Grade 3 ALT and Grade 4 AST laboratory elevations after Day 122. There were no discontinuations due to AEs and no drug-related deaths.<sup>16</sup> Overall, RAL was well tolerated when administered as a film-coated tablet twice daily in participants aged 6 years to <19 years and as chewable tablets at a dose of approximately 6 mg/kg twice daily in participants aged 2 years to <12 years, with favorable virologic and immunologic responses.<sup>21</sup>

## Children Aged ≥4 Weeks to <2 Years

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for RAL oral suspension in combination with an optimized background ARV regimen. All participants had previously received ARV drugs to prevent perinatal transmission and/or treat HIV, and 69% had baseline plasma HIV RNA exceeding 100,000 copies/mL. PK targets for Cohort IV (6 months to <2 years) and Cohort V (4 weeks to <6 months) were modified to a GM AUC<sub>0-12h</sub> of 14 μM·h to 45 μM·h and a GM C<sub>12h</sub> ≥75 nM (33.3 ng/mL). These targets were modified so that an estimated >90% of patients would have C<sub>12h</sub> above the 45 nM threshold. By Week 48, two participants experienced AEs that were thought to be related to the study drug: one patient experienced a serious erythematous rash that resulted in permanent discontinuation of RAL, and one patient experienced immune reconstitution inflammatory syndrome. Virologic success, defined as ≥1 log<sub>10</sub> decline in HIV RNA or <400 copies/mL at 48 weeks, was achieved in >87% of participants. At 48 weeks of follow up, 45.5% of participants had HIV RNA <50 copies/mL and mean CD4 count increases of 527.6 cells/mm<sup>3</sup> (7.3%). Four participants in Cohort 4 experienced virologic failure by Week 48, and one participant had a RAL-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately RAL 6 mg/kg twice daily, were well tolerated and had good efficacy.<sup>15</sup>

## Long-Term Follow Up in Children

The IMPAACT P1066 study team reported results regarding the safety and efficacy of different RAL formulations at 240 weeks in children enrolled in this multicenter trial.<sup>22</sup> Eligible participants were children aged 4 weeks to 18 years who had previously been treated with ART and who were experiencing virologic failure at the time of enrollment. RAL was added to an optimized ARV regimen in all participants. RAL was well tolerated, and few serious clinical or laboratory safety events were noted during the study.<sup>22</sup>

The proportion of participants who achieved virologic success at 240 weeks varied by the RAL formulation used: 19 of 43 children (44.2%) who received RAL 400-mg tablets; 24 of 31 children (77.4%) who received chewable tablets; and 13 of 15 children (86.7%) who received the oral granules for suspension. RAL resistance was documented in 19 of 50 patients (38%) who experienced virologic rebound after initial suppression. These results suggest that younger children with less treatment experience are more likely to have sustained virologic suppression, whereas older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to RAL. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the RAL 400-mg tablets.<sup>22</sup>

## Neonates Aged <4 Weeks

RAL is metabolized by UGT1A1, the same enzyme that is responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. Washout PKs of RAL in neonates born to pregnant women with HIV were studied in [IMPAACT P1097](#).<sup>23</sup> The neonatal plasma half-life of RAL was highly variable, ranging from 9.3 to 184 hours. This suggests that neonatal development may impact UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of RAL. RAL competes with unconjugated bilirubin for albumin binding sites. When RAL plasma concentrations are extremely high, unconjugated bilirubin may be displaced from albumin by RAL and cross the blood–brain barrier, leading to bilirubin-induced neurologic dysfunction. The effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant, unless concentrations that are 50-fold to 100-fold higher than typical peak concentrations are reached (approximately 5,000 ng/mL).<sup>24</sup>

IMPAACT P1110 was a Phase 1 multicenter trial that enrolled full-term neonates with or without *in utero* RAL exposure at risk of acquiring HIV. RAL-exposed neonates were those whose mothers received RAL within 2 to 24 hours of delivery. For RAL-exposed neonates, the initial dose of RAL was delayed until 12 to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two RAL doses that were administered 1 week apart, and Cohort 2 infants received daily RAL doses for the first 6 weeks of life. PK data from Cohort 1 and from older infants and children were combined in a population PK model, and simulations were used to select the following RAL dosing regimen for evaluation in infants in Cohort 2: RAL 1.5 mg/kg daily, starting within 48 hours of life and continuing through Day 7; RAL 3 mg/kg twice daily on Days 8 to 28 of life; and RAL 6 mg/kg twice daily after 4 weeks of age.<sup>25</sup> Protocol exposure targets for each participant were AUC from time zero to 24 hours after drug administration ( $AUC_{0-24hr}$ ) 12 mg·h/L to 40 mg·h/L,  $AUC_{0-12hr}$  6 mg·h/L to 20 mg·h/L, and  $C_{12h}$  or  $C_{24h}$  >33 ng/mL. Safety was assessed using clinical and laboratory evaluations.<sup>23,26,27</sup>

Twenty-six RAL-naïve infants and 10 RAL-exposed infants were enrolled in Cohort 2; 25 RAL-naïve infants and 10 RAL-exposed infants had evaluable PK results and safety data. Results for the RAL-naïve infants and RAL-exposed infants who were enrolled in Cohort 2 are contained in Table B below.<sup>27</sup>



**Table B. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naive and Raltegravir-Exposed Neonates**

PK Parameter	Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Naive (n = 25) <sup>d</sup>	Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Exposed (n = 10)	Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Naive (n = 24) <sup>e</sup>	Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Exposed (n = 10) <sup>f</sup>
	GM (CV%)	GM (CV%)	GM (CV%)	GM (CV%)
AUC <sub>0–24h</sub> (mg·h/L) <sup>a</sup>	38.2 (42.0%)	42.9 (25.3%)	—	—
AUC <sub>0–12h</sub> (mg·h/L)	—	—	14.3 (49.5%)	18.3 (62.8%)
C <sub>trough</sub> (ng/mL) <sup>b</sup>	948 (84.0%)	946 (74.0%)	176 (162.1%)	274 (176.4%)
C <sub>max</sub> (ng/mL) <sup>c</sup>	2,350 (36.5%)	2,565 (23.1%)	2,849 (47.5%)	3,667 (46.3%)
T <sub>max</sub> (hours)	5.4 (71.5%)	3.8 (88.8%)	2.3 (77.1%)	1.9 (52.3%)
T <sub>1/2</sub> (hours)	15.8 (101.4%)	14.4 (69.5%)	2.5 (34.1%)	2.9 (20.7%)

<sup>a</sup> AUC targets: AUC<sub>0–24h</sub> 12–40 mg·h/L and AUC<sub>0–12h</sub> 6–20 mg·h/L.

<sup>b</sup> C<sub>trough</sub> concentration >33 ng/mL. For initial dose, the last measurable plasma concentration collected at 24 hours was used. For Days 15–18, C<sub>12h</sub> was estimated when the 12-hours-post-dose sample was collected earlier than 12 hours after dosing (the protocol specified a sample collection time of 8–12 hours postdose).

<sup>c</sup> C<sub>max</sub> <8,724 ng/mL

<sup>d</sup> AUC<sub>0–24h</sub> could not be estimated for one infant.

<sup>e</sup> AUC<sub>0–12h</sub> and C<sub>trough</sub> could not be estimated for one infant with delayed absorption.

<sup>f</sup> AUC<sub>0–12h</sub> and C<sub>max</sub> could not be estimated for one infant with incomplete sample collection.

**Key:** AUC = area under the curve; AUC<sub>0–12h</sub> = AUC from time zero to 12 hours after drug administration; AUC<sub>0–24h</sub> = AUC from time zero to 24 hours after drug administration; C<sub>max</sub> = maximum concentration; C<sub>trough</sub> = trough concentration; CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic; RAL = raltegravir; T<sub>1/2</sub> = half-life; T<sub>max</sub> = time to reach maximum concentration

Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for up to 6 weeks from birth and followed for a total of 24 weeks. All GM protocol exposure targets were met. In some infants, AUC<sub>0–24h</sub> following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in RAL metabolism during the first week of life. The PK targets and the safety guidelines were met for both RAL-naive and RAL-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory AEs were reported among the RAL-naive infants: Grade 4 transient neutropenia occurred in one infant who received a zidovudine-containing regimen; two bilirubin elevations (one Grade 1 and one Grade 2) were considered nonserious and did not require specific therapy.<sup>7</sup> Among the RAL-exposed infants, four infants exhibited Grade 3 or 4 toxicities: anemia in one infant, neutropenia in one infant, and hyperbilirubinemia in two infants. No specific therapy was required to treat these toxicities, and no infants required phototherapy or exchange transfusion for hyperbilirubinemia.

Results from IMPAACT P1110 confirmed the PK modeling and simulation submitted for FDA approval and labeling. Neonates born to mothers who received RAL 2 to 24 hours prior to delivery

should have their first dose of RAL delayed until 24 to 48 hours after birth.<sup>26,27</sup> The timing of administration of the initial dose of RAL to infants born to patients receiving DTG- or bicitegravir-containing regimens has not been studied. In a single case report of a neonate born to a mother receiving an intensified regimen of DTG 50 mg twice daily for viremia close to the time of delivery, prolonged neonatal DTG concentrations were observed.<sup>28</sup> These findings suggest that a similar delay in the first dose of RAL until 24 to 48 hours after birth may be indicated in neonates born to patients receiving an INSTI-containing oral regimen to avoid potential toxicity. Results of ongoing studies [IMPAACT 2023](#) (DTG neonatal PK and safety study) and [IMPAACT 2026](#) (washout PK in infants born to mothers receiving bicitegravir) may provide PK data that can inform future recommendations.

The current RAL dosing regimen with two dose changes in the first month of life may be challenging for some families. To simplify medication teaching and minimize dosing changes, some experts increase to the 3 mg/kg twice-daily dose on Day 4 or 5 of life. Because many infants receiving RAL as part of presumptive HIV therapy will have a longer hospital stay following birth by cesarean section, this dosing change can generally be made at the time of hospital discharge.

RAL can be safely administered to full-term infants using the daily dosing regimen that was studied in IMPAACT P1110. This regimen **is not recommended** for use in preterm infants. RAL elimination kinetics in preterm and low-birth-weight neonates after maternal dosing was studied in IMPAACT P1097.<sup>29</sup> Sixteen mothers and their 18 low-birth-weight neonates (<2.5 kg) were enrolled. Median (range) RAL elimination half-life was 24.4 hours (10.1–83) hours (n = 17). A PK model incorporating slower clearance in preterm neonates demonstrated that a reduction in RAL dosing is required in this population.<sup>29</sup>

Two case reports of preterm infants who received RAL to prevent perinatal transmission have been published.<sup>30,31</sup> These case reports involved one infant born at a gestational age of 24 weeks and 6 days who weighed 800 g and another infant born at 33 weeks gestation who weighed 1,910 g. In both infants, intermittent dosing of RAL was done using real-time therapeutic drug monitoring in the neonatal intensive care unit.<sup>30,31</sup> Less-frequent dosing was required because RAL elimination was significantly delayed in these preterm infants. RAL PKs and safety must be studied in preterm infants before RAL can be safely used without real-time PK monitoring in this population.

## Formulations

The PK of RAL in adult patients with HIV who swallowed intact 400-mg tablets were compared with those observed in patients who chewed the 400-mg, film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher among patients who chewed the tablets, although the palatability was rated as poor.<sup>32</sup> In adult volunteers, the PK of RAL 800 mg taken once daily by chewing was compared with the PK of two doses of RAL 400 mg taken every 12 hours by swallowing. Participants who took RAL by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets according to current recommendations.<sup>33</sup> According to the manufacturer, the film-coated tablets must be swallowed whole.

The RAL chewable tablet and oral suspension have higher oral bioavailability than the 400-mg, film-coated tablet, according to a comparative study in healthy adult volunteers.<sup>34</sup> Compared with the RAL 400-mg tablet formulation, the RAL 600-mg tablet has higher relative bioavailability.<sup>7,35</sup> Interpatient and inpatient variability for PK parameters of RAL are considerable, especially with the film-coated tablets.<sup>7,36</sup> Because of differences in the bioavailability of various formulations, the

dosing recommendations for each formulation differ, and the formulations **are not interchangeable**. When prescribing RAL, clinicians should refer to the appropriate dosing table for the chosen formulation. The use of RAL chewable tablets as dispersible tablets in children aged <2 years has been studied in [IMPAACT P1101](#) for infants and toddlers with TB/HIV coinfection who received rifampin as part of their TB treatment. The use of RAL chewable tablets dispersed in water at a dose of RAL 12 mg/kg per dose twice daily safely achieved PK targets.<sup>2,37</sup> The RAL chewable tablets are now approved for use in infants and young children 4 weeks of age and older and weighing at least 2 kg.<sup>38</sup> An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including water, apple juice, and breast milk.<sup>38</sup> The chewable tablets may be crushed and mixed with a small amount of liquid to facilitate administration (see Special Instructions above).

Palatability was evaluated as part of IMPAACT P1066. Both chewable tablets and oral granules for suspension were thought to have acceptable palatability. Seventy-three percent of those surveyed reported no problems with chewable tablets; 82.6% reported no problems with administering the oral granules.<sup>15,16</sup> The acceptability and feasibility of administering RAL granules for oral suspension in a low-resource setting has been studied in clinics in South Africa and Zimbabwe. With proper training by health care personnel, caregivers were able to prepare the suspension safely and accurately.<sup>39,40</sup>

# Appendix A: Pediatric Antiretroviral Drug Information

## Pharmacokinetic Enhancers

Cobicistat (COBI, Tybost)

Ritonavir (RTV, Norvir)

## Cobicistat (COBI, Tybost)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Tablet: 150 mg</p> <p><b>Fixed-Dose Combination (FDC) Tablets</b></p> <ul style="list-style-type: none"> <li>[Evotaz] Atazanavir 300 mg/cobicistat 150 mg</li> <li>[Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg</li> <li>[Prezcobix] Darunavir 800 mg/cobicistat 150 mg</li> <li>[Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg</li> <li>[Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg</li> </ul> <p>When using FDC tablets, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Cobicistat (COBI) Is a Pharmacokinetic Enhancer</b></p> <ul style="list-style-type: none"> <li>The only use of COBI is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase strand transfer inhibitors. COBI is <b>not interchangeable</b> with ritonavir (RTV) and has no antiviral activity.</li> </ul> <p><b>Child and Adolescent (Weighing <math>\geq 35</math> kg) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>COBI 150 mg with atazanavir (ATV) 300 mg administered at the same time with food</li> </ul> <p><b>Child and Adolescent (Weighing <math>\geq 40</math> kg) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>COBI 150 mg with darunavir (DRV) 800 mg administered at the same time with food</li> </ul> <p>[Evotaz] ATV/COBI</p> <p><i>Child and Adolescent (Weighing <math>\geq 35</math> kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with food</li> <li>Use in combination with other antiretroviral (ARV) drugs.</li> </ul>	<ul style="list-style-type: none"> <li>COBI is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces the estimated glomerular filtration rate, with no change in glomerular function.</li> </ul>
	<ul style="list-style-type: none"> <li>COBI 150 mg is <b>not interchangeable</b> with RTV, but it has a PK-boosting effect that is comparable to RTV 100 mg.</li> <li>Drug interactions may differ between RTV and COBI, because COBI is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of RTV.</li> <li><b>Do not administer</b> COBI with RTV or with FDC tablets that contain COBI.</li> <li>COBI is <b>not recommended</b> for use with more than one ARV drug that requires PK enhancement (e.g., EVG used in combination with a PI).</li> <li>Using COBI with PIs other than once-daily ATV 300 mg or DRV 800 mg is <b>not recommended</b>.</li> </ul>

<p><b>[Genvoya] Elvitegravir (EVG)/COBI/Emtricitabine (FTC)/ Tenofovir Alafenamide (TAF)</b></p> <p><i>Child (Weighing ≥14 to &lt;25 kg)</i></p> <ul style="list-style-type: none"> <li>Limited data currently exist on the appropriate dose of Genvoya in children weighing ≥14 kg to &lt;25 kg. Studies are currently being conducted to assess the safety and efficacy of a low-dose tablet with EVG 90 mg/COBI 90 mg/ FTC 120 mg/TAF 6 mg.</li> </ul> <p><i>Child and Adolescent (Weighing ≥25 kg) and Adult Dose</i></p> <ul style="list-style-type: none"> <li>One tablet once daily with food</li> </ul>	<ul style="list-style-type: none"> <li>Patients with a confirmed increase in serum creatinine &gt;0.4 mg/dL from baseline should be closely monitored for renal safety.</li> <li>When using COBI in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while the patient is receiving therapy (see <a href="#">Table 17i. Nephrotoxic Effects</a>). In patients who are at risk of renal impairment, serum phosphate also should be monitored.</li> <li>For information on crushing and cutting tablets, see <a href="#">Information on Crushing and Liquid Drug Formulations</a> from Toronto General Hospital.</li> </ul>
<p><b>[Prezcobix] DRV/COBI</b></p> <p><i>Child and Adolescent (Weighing ≥40 kg) and Adult Dose</i></p>	<p><b>Metabolism/Elimination</b></p>
<ul style="list-style-type: none"> <li>One tablet once daily with food</li> <li>Use in combination with other ARV drugs.</li> </ul>	<ul style="list-style-type: none"> <li>COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.</li> </ul>
<p><b>[Stribild] EVG/COBI/FTC/Tenofovir Disoproxil Fumarate (TDF)</b></p> <p><i>Child and Adolescent (Weighing ≥35 kg) and Adult Dose</i></p>	<p><b>COBI Dosing in Patients with Hepatic Impairment</b></p>
<ul style="list-style-type: none"> <li>One tablet once daily with food</li> <li>The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.</li> </ul>	<ul style="list-style-type: none"> <li>COBI does not require dose adjustment in patients with mild-to-moderate hepatic impairment. No data are available in patients with severe hepatic impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.</li> <li>Genvoya, Prezcobix, Stribild, and Symtuza <b>are not recommended</b> in patients with severe hepatic impairment.</li> <li>Evotaz <b>is not recommended</b> in patients with any degree of hepatic impairment.</li> </ul>
<p><b>[Symtuza] DRV/COBI/FTC/TAF</b></p> <p><i>Child and Adolescent (Weighing ≥40 kg) and Adult Dose</i></p>	<p><b>COBI Dosing in Patients with Renal Impairment</b></p>
<ul style="list-style-type: none"> <li>One tablet once daily with food</li> </ul>	<ul style="list-style-type: none"> <li>COBI does not require a dose adjustment in patients with renal impairment, including those with severe renal impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.</li> <li>The use of COBI plus TDF <b>is not recommended</b> in patients with creatinine clearance (CrCl) &lt;70 mL/min. Dose adjustments for TDF are required for patients with CrCl &lt;50 mL/min, and the necessary dose adjustments for TDF when this drug is used with COBI have not been established in this group of patients.</li> <li>Genvoya <b>is not recommended</b> in patients with estimated CrCl 15 to &lt;30 mL/min, or in patients with estimated CrCl &lt;15 mL/min who are not receiving chronic hemodialysis.</li> </ul>

	<ul style="list-style-type: none"> <li>• Stribild <b>should not be initiated</b> in patients with estimated CrCl &lt;70 mL/min and should be discontinued in patients with estimated CrCl &lt;50 mL/min. The dose adjustments required for <b>FTC</b> and TDF in these patients cannot be achieved with an FDC tablet.</li> <li>• Symtuza is <b>not recommended</b> in patients with estimated CrCl &lt;30 mL/min.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Metabolism of cobicistat (COBI) is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. COBI also inhibits breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1. Unlike ritonavir, COBI does not demonstrate any enzyme-inducing effects. The potential exists for multiple drug interactions when using COBI. Before COBI is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs. Coadministration of medications that induce or inhibit CYP3A4 may respectively decrease or increase exposures of COBI and coformulated antiretroviral (ARV) medications. Coadministration of medications that are CYP3A4 substrates may result in clinically significant adverse reactions that are severe, life-threatening, or fatal, or may result in loss of therapeutic effect if dependent on conversion to an active metabolite due to CYP3A4 inhibition by COBI.<sup>1</sup>
- *Nucleoside reverse transcriptase inhibitors:* COBI is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with COBI produces tenofovir (TFV) exposures that are similar to those produced by TAF 25 mg without COBI.<sup>2</sup> COBI increases plasma TFV exposures by 23% when it is coadministered with TDF; thus, renal safety should be monitored in patients who are receiving this combination.<sup>1,3</sup>
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine **should not be used** with COBI.
- *Protease inhibitors:* Using COBI as a dual booster for elvitegravir (EVG) and darunavir (DRV) has been studied in people with and without HIV, and the evidence is conflicting. When EVG plus COBI plus DRV was administered to people without HIV, the trough concentration ( $C_{\text{trough}}$ ) of EVG was 50% lower than the  $C_{\text{trough}}$  seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) without DRV.<sup>4</sup> When EVG/c/FTC/TAF was administered with DRV to patients with HIV, both DRV and EVG concentrations were comparable to those seen in historic controls.<sup>5</sup>
- *Integrase inhibitors:* In one small study, dolutegravir (DTG)  $C_{\text{trough}}$  was 107% higher when DTG was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.<sup>6</sup> Bictegravir (BIC) area under the curve increases 74% when BIC is administered with DRV/c.<sup>7</sup>



- *Corticosteroids:* Increased serum concentrations of corticosteroids can occur when corticosteroids and COBI are coadministered; this can lead to clinically significant adrenal suppression. Adrenal suppression occurs regardless of whether the corticosteroids are administered orally or by some other route (e.g., intranasal, inhaled, interlaminar, intraarticular) and regardless of whether the corticosteroids are administered routinely or intermittently. A possible exception is beclomethasone, which appears to be a relatively safe option with inhaled or intranasal administration.<sup>8,9</sup>

## Major Toxicities

- *More common:* Nausea, vomiting, diarrhea, abdominal pain, anorexia
- *Less common (more severe):* New onset renal impairment or worsening of renal impairment when used with TAF or TDF, rhabdomyolysis, increased amylase and lipase levels

## Resistance

Not applicable because COBI has no antiviral activity.

## Pediatric Use

### *Approval*

COBI is a pharmacokinetic (PK) enhancer of ARV drugs that is available as a single agent or a component of fixed-dose combination products. COBI, as a component of Stribild, is approved by the U.S. Food and Drug Administration (FDA) at the adult dose for use in children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg.<sup>10</sup> The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild to those with a sexual maturity rating of 4 or 5. COBI, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing  $\geq 25$  kg.<sup>11</sup> The FDA has not approved COBI as a component of Genvoya for use in children weighing  $< 25$  kg, but an ongoing PK, safety, and efficacy study is underway with a low-dose tablet in children weighing  $\geq 14$  kg to  $< 25$  kg (see the [Elvitegravir](#) section). COBI alone (as Tybost) is approved by the FDA at the adult dose for use in children weighing  $\geq 35$  kg when used in combination with ATV, and in children weighing  $\geq 40$  kg when used in combination with DRV.<sup>1</sup> COBI, coformulated with ATV (as Evotaz),<sup>12</sup> is approved by the FDA at the adult dose for use in children and adolescents weighing  $\geq 35$  kg. COBI, coformulated with DRV (as Prezcofix)<sup>13</sup> and as a component of Symtuza,<sup>14</sup> is approved by the FDA at the adult dose in children and adolescents weighing  $\geq 40$  kg.

## Ritonavir (RTV, Norvir)

Updated: June 27, 2024

Reviewed: June 27, 2024

Formulations	
<p>Oral Powder: 100 mg per packet</p> <p>Tablet: 100 mg</p> <p><b>Generic Formulation</b></p> <ul style="list-style-type: none"> <li>100-mg tablet</li> </ul> <p><b>Fixed-Dose Combination (FDC) Solution</b></p> <ul style="list-style-type: none"> <li>[Kaletra] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.</li> </ul> <p><b>FDC Tablets</b></p> <ul style="list-style-type: none"> <li>[Kaletra] Lopinavir 100 mg/ritonavir 25 mg</li> <li>[Kaletra] Lopinavir 200 mg/ritonavir 50 mg</li> </ul> <p>When using FDC tablets or solution, refer to other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the individual components of the FDC. See also <a href="#">Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents</a>.</p> <p>For additional information, see <a href="#">Drugs@FDA</a> or <a href="#">DailyMed</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Ritonavir (RTV) as a Pharmacokinetic Enhancer</b></p> <ul style="list-style-type: none"> <li>RTV is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs). The recommended dose of RTV varies and is specific to the drug combination selected. See other sections of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information about the recommended doses of RTV to use with specific PIs. RTV has antiviral activity, but it is not used as an antiviral agent; instead, it is used as a PK enhancer of other PIs.</li> </ul> <p><b>Formulation Considerations</b></p> <ul style="list-style-type: none"> <li>RTV oral powder should be used only for dosing increments of 100 mg and cannot be used for doses &lt;100 mg.</li> </ul> <p><b>[Kaletra] Lopinavir/Ritonavir</b></p> <p><i>Infant, Child, Adolescent, and Adult Dose</i></p> <ul style="list-style-type: none"> <li>See the <a href="#">Lopinavir/Ritonavir</a> section of <a href="#">Appendix A. Pediatric Antiretroviral Drug Information</a> for information.</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea</li> <li>Hyperlipidemia, especially hypertriglyceridemia</li> <li>Hepatitis</li> <li>Hyperglycemia</li> <li>Fat maldistribution</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>Administer RTV with food to increase absorption and reduce the likelihood and severity of GI adverse events.</li> <li><b>Do not administer</b> RTV with cobicistat (COBI) or drugs that contain COBI (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).</li> <li>RTV oral powder should be mixed with a soft food (e.g., applesauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help</li> </ul>

	<p>mitigate the bitter taste. Administer or discard the mixture within 2 hours of mixing.</p> <p><b>To Increase Tolerability of RTV Oral Powder in Children</b></p> <ul style="list-style-type: none"> <li>• Mix the powder with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.</li> <li>• Before administering RTV, give a child ice chips, an ice pop, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a nonallergic child peanut butter or hazelnut chocolate spread to coat the mouth.<sup>1</sup></li> <li>• After administration, give foods with strong tastes (e.g., maple syrup, cheese).</li> <li>• Check a child's food allergy history before making these recommendations.</li> <li>• Counsel caregivers or patients that the bad taste will not be completely masked.</li> </ul> <p style="text-align: center;"><b>Metabolism/Elimination</b></p> <ul style="list-style-type: none"> <li>• Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein.</li> </ul> <p><b>RTV Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>• RTV is primarily metabolized by the liver.</li> <li>• No dose adjustment is necessary in patients with mild or moderate hepatic impairment.</li> <li>• No data exist on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#).

1. *Metabolism:* Ritonavir (RTV) is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, RTV is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein. There is potential for multiple drug interactions with RTV.
2. Before RTV is administered, a patient's medication profile should be reviewed carefully for potential interactions with RTV and overlapping toxicities with other drugs.

3. RTV and cobicistat **are not interchangeable**. The potential drug interactions for these drugs are different.<sup>2</sup>
4. Avoid concomitant use of corticosteroids, including intranasal or inhaled fluticasone or inhaled budesonide. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.<sup>3,4</sup> Use caution when prescribing RTV with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking RTV requires an inhaled or intranasal corticosteroid.<sup>5,6</sup> Iatrogenic Cushing's syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between RTV and local injection of triamcinolone has occurred.<sup>7,8</sup> See [Table 24a. Drug Interactions Between Protease Inhibitors and Other Drugs](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) for additional information.

## Major Toxicities

5. *More common*: Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, abnormal lipid levels
6. *Less common (more severe)*: Exacerbation of chronic liver disease, fat maldistribution
7. *Rare*: New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis. Cases of hepatitis, including life-threatening cases, have been reported. Allergic reactions, including bronchospasm, urticaria, and angioedema have occurred. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.<sup>9</sup>

## Resistance

Resistance to RTV is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

## Pediatric Use

### *Approval*

RTV has been approved by the U.S. Food and Drug Administration for use in the pediatric population.

### *Effectiveness in Practice*

Use of RTV as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended**. In both children and adults, RTV is recommended as a PK enhancer for use with other PIs. RTV is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PI.

### *Dosing*

Dosing regimens for RTV-boosted darunavir and atazanavir and coformulated lopinavir/ritonavir (LPV/r) are available for pediatric patients. For more information about individual PIs, see other sections of [Appendix A: Pediatric Antiretroviral Drug Information](#).

## ***Toxicity***

Full-dose RTV has been shown to prolong the PR interval in a study of healthy adults who were given RTV 400 mg twice daily.<sup>9</sup> Potentially life-threatening arrhythmias have been reported in premature infants who were treated with LPV/r; therefore, the use of LPV/r is generally not recommended before a gestational age of 42 weeks (see the [Lopinavir/Ritonavir](#) section).<sup>10,11</sup> Coadministration of RTV with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how coadministering any of these drugs with RTV will affect the PR interval. In addition, RTV should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

# Appendix A: Pediatric Antiretroviral Drug Information

## Archived Drugs

The Archived Drugs section of Appendix A: Pediatric Antiretroviral Drug Information provides access to the last updated versions of drug sections that are no longer being reviewed by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel). Archived Drugs includes older antiretroviral drugs that the Panel does not recommend for use in children because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data.

[Didanosine \(ddl, Videx\)](#)

[Enfuvirtide \(T-20, Fuzeon\)](#)

[Fosamprenavir \(FPV, Lexiva\)](#)

[Indinavir \(IDV, Crixivan\)](#)

[Nelfinavir \(NFV, Viracept\)](#)

[Saquinavir \(SQV, Invirase\)](#)

[Stavudine \(d4t, Zerit\)](#)

[Tipranavir \(TPV, Aptivus\)](#)

## Didanosine (ddl, Videx)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations									
<p><b>Pediatric Oral Solution:</b> 10 mg/mL</p> <p><b>Enteric-Coated (EC) Delayed-Release Capsules (EC Beadlets):</b> 125 mg, 200 mg, 250 mg, and 400 mg</p> <p><b>Generic Formulations</b></p> <p><b>Delayed-Release Capsules:</b> 125 mg, 200 mg, 250 mg, and 400 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>									
Dosing Recommendations	Selected Adverse Events								
<p><b>Note:</b> Didanosine is <b>no longer recommended</b> by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV for use in children due to higher rates of adverse effects than other NRTIs.</p> <p><b>Neonate/Infant Dose (Aged 2 Weeks to &lt;3 Months)</b></p> <ul style="list-style-type: none"> <li>50 mg/m<sup>2</sup> of body surface area every 12 hours. See dosing section below for justification of this dose.</li> </ul> <p><b>Infant Dose (Aged ≥3 Months to 8 Months)</b></p> <ul style="list-style-type: none"> <li>100 mg/m<sup>2</sup> of body surface area every 12 hours</li> </ul> <p><b>Pediatric Dose of Oral Solution (Aged &gt;8 Months)</b></p> <ul style="list-style-type: none"> <li>120 mg/m<sup>2</sup> of body surface area every 12 hours</li> <li>Dose range: 90–150 mg/m<sup>2</sup> of body surface area every 12 hours. Do not exceed maximum adult dose; see table below.</li> <li>In treatment-naïve children aged 3 years to 21 years, 240 mg/m<sup>2</sup> of body surface area once daily (oral solution or capsules) has resulted in viral suppression.</li> </ul> <p><b>Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥20 kg)</b></p> <table border="1"> <thead> <tr> <th>Body Weight</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>20 kg to &lt;25 kg</td> <td>200 mg once daily</td> </tr> <tr> <td>25 kg to &lt;60 kg</td> <td>250 mg once daily</td> </tr> <tr> <td>≥60 kg</td> <td>400 mg once daily</td> </tr> </tbody> </table>	Body Weight	Dose	20 kg to <25 kg	200 mg once daily	25 kg to <60 kg	250 mg once daily	≥60 kg	400 mg once daily	<ul style="list-style-type: none"> <li>Peripheral neuropathy</li> <li>Diarrhea, abdominal pain, nausea, vomiting</li> <li>Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (the risk is increased when didanosine is used in combination with stavudine).</li> <li>Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir disoproxil fumarate or stavudine)</li> <li>Non-cirrhotic portal hypertension</li> <li>Retinal changes, optic neuritis</li> <li>Insulin resistance/diabetes mellitus</li> </ul>
Body Weight	Dose								
20 kg to <25 kg	200 mg once daily								
25 kg to <60 kg	250 mg once daily								
≥60 kg	400 mg once daily								
	Special Instructions								
	<ul style="list-style-type: none"> <li>Administer didanosine on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).</li> <li>Didanosine powder for oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration.</li> <li>Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.</li> </ul>								



Adolescent and Adult Dose		Metabolism/Elimination
<b>Body Weight</b>	<b>Dose</b>	<ul style="list-style-type: none"> <li>Renal excretion 50%</li> <li>Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.</li> </ul>
<60 kg	250 mg once daily	
≥60 kg	400 mg once daily	
<b>Pediatric and Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate</b> <ul style="list-style-type: none"> <li>This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic nonresponse, high rates of early virologic failure, and rapid selection of resistance mutations (see the <a href="#">Adult and Adolescent Guidelines</a>).</li> </ul>		

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Absorption:** Antacids in didanosine oral solution can decrease the absorption of a number of medications if given at the same time. Avoid giving other medications concurrently with didanosine oral solution.
- Mechanism unknown:** Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir disoproxil fumarate (TDF). This combination should be avoided.
- Renal elimination:** Drugs that decrease renal function can decrease didanosine clearance.
- Overlapping toxicities:** The combination of stavudine with didanosine may result in enhanced toxicity. This combination should be avoided (see the Major Toxicities section below).

## Major Toxicities

- More common:** Diarrhea, abdominal pain, nausea, vomiting
- Less common (more severe):** Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported, and are more common when didanosine is used in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with TDF or stavudine) can occur. Increased liver enzymes, retinal depigmentation, and optic neuritis have been reported. Decreases in CD4 T lymphocyte counts have been reported when didanosine is used in combination with TDF.
- Rare:** Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use.<sup>1</sup>
- Possible risk of cancer after in-utero exposure:** In a study of 15,163 children without HIV infection who were exposed to at least one nucleoside reverse transcriptase inhibitor (NRTI) *in utero*, 21 cancers were identified. Didanosine accounted for only 10% of prescriptions but was associated with one-third of identified cancers, and, in multivariate analysis, didanosine was

associated with a 5.5-fold (95% CI, 2.1–14.4) increased risk of cancer with first-trimester exposure.<sup>2</sup> Pregnant adolescents or sexually active female adolescents on didanosine should be cautioned about this risk.

## Resistance

The International AIDS Society–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*

Although didanosine is a Food and Drug Administration (FDA)-approved NRTI for use in children as part of antiretroviral therapy, it **is not recommended** for in children due to its significant toxicity and the availability of safer agents.

## Dosing

### *Standard Dose in Children Aged >8 Months*

The standard dose of didanosine oral solution in children aged >8 months is 120 mg/m<sup>2</sup> of body surface area twice daily.<sup>3,4</sup> Doses higher than 180 mg/m<sup>2</sup> of body surface area twice daily are associated with increased toxicity.<sup>5</sup>

### *Special Considerations for Children Aged 2 Weeks to <8 Months*

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m<sup>2</sup> of body surface area per dose twice daily. However, because pharmacokinetic (PK) differences in younger infants (aged 2 weeks–3 months) compared with older children raise concerns for increased toxicity in this younger age group, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends a dose of 50 mg/m<sup>2</sup> of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m<sup>2</sup> of body surface area per dose twice daily at 3 months, and finally increasing to 120 mg/m<sup>2</sup> of body surface area per dose twice daily at age 8 months (as discussed above).

### *Frequency of Administration (Once Daily or Twice Daily)*

In those aged >3 years, a once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing of 240 mg/m<sup>2</sup> of body surface area.<sup>6</sup>

### *Food Restrictions*

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently, and it may decrease medication adherence by increasing regimen complexity. A comparison showed that systemic exposure measured by area under the curve was similar whether didanosine oral solution was given to children with or without food; absorption of didanosine administered with food was slower and elimination more prolonged.<sup>7</sup>

To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food.<sup>8,9</sup> A European study dosed didanosine oral solution as part of a four-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction. The study showed good virologic outcome with up to 96 weeks of follow-up.<sup>10</sup>

## Enfuvirtide (T-20, Fuzeon)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations	
<p><b>Lyophilized Powder for Injection:</b> 108-mg vial of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.</p> <p><b>Convenience Kit:</b> 60 single-use vials of enfuvirtide (108-mg vial reconstituted as 90 mg/mL), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>	
Dosage Recommendations	Selected Adverse Events
<p><b>Pediatric and Adolescent Dose (Aged 6–16 Years)</b></p> <p><i>Children Aged &lt;6 Years</i></p> <ul style="list-style-type: none"> <li>Not approved for use in children aged &lt;6 years</li> </ul> <p><i>Children Aged ≥6 Years</i></p> <ul style="list-style-type: none"> <li>2 mg/kg (maximum dose 90 mg [1 mL]) twice daily injected subcutaneously (SQ) into the upper arm, anterior thigh, or abdomen</li> </ul> <p><b>Adolescent (Aged &gt;16 Years) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>90 mg (1 mL) twice daily injected SQ into the upper arm, anterior thigh, or abdomen</li> </ul>	<ul style="list-style-type: none"> <li>Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in up to 98% of patients.</li> <li>Increased rate of bacterial pneumonia (unclear association).</li> <li>Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is <b>not recommended</b>.</li> </ul>
	Special Instructions

	<ul style="list-style-type: none"> <li>Advise patients/caregivers of the possibility of a HSR; instruct them to discontinue treatment and seek immediate medical attention if a patient develops signs and symptoms consistent with a HSR.</li> </ul>
	<b>Metabolism/Elimination</b>
	<ul style="list-style-type: none"> <li>Catabolism to constituent amino acids.</li> </ul>

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

There are no known significant drug interactions with enfuvirtide.

## Major Toxicities

- More common:* Almost all patients (87% to 98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days but was >7 days in 24% of patients.
- Less common (more severe):* Increased rate of bacterial pneumonia (unclear association).<sup>1</sup> Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.
- Rare:* Hypersensitivity reactions (HSRs) (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.
- Pediatric specific:* Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).<sup>2</sup>

## Resistance

The International AIDS Society–USA maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

Resistance testing must be ordered specifically for fusion inhibitors, as it is not performed on routine genotypic or phenotypic assays.

## Pediatric Use

### *Approval*

Although enfuvirtide is Food and Drug Administration (FDA)-approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high

rate of injection site reactions. Use in deep salvage regimens<sup>3</sup> has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

### ***Pharmacokinetics***

A single-dose pharmacokinetic evaluation study of enfuvirtide, given SQ to 14 children with HIV aged 4 years to 12 years (PACTG 1005), identified that enfuvirtide 60 mg/m<sup>2</sup> of body surface area per dose resulted in a target trough concentration that approximated the equivalent of a 90-mg dose delivered SQ to an adult (1000 mg/mL).<sup>4</sup> In a second pediatric study of 25 children aged 5 years to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily yielded drug concentrations similar to 60 mg/m<sup>2</sup> of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.<sup>5</sup> The FDA-recommended dose of enfuvirtide for children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

### ***Efficacy***

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m<sup>2</sup> per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a >1.0<sub>log</sub> reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively. However, only 36% of children maintained virologic suppression (>1.0<sub>log</sub> decrease in HIV RNA) at Week 96. Most children had local injection site reactions.<sup>6</sup> Significant improvements in CD4 T lymphocyte (CD4) cell percentages and height z scores were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase 1/2 study of enfuvirtide (2.0 mg/kg SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 log<sub>10</sub> copies/mL (n = 32) and increase in CD4 cell count was 106 cells/mm<sup>3</sup> (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm<sup>3</sup> in children and 84 cells/mm<sup>3</sup> in adolescents. Local skin reactions were common in all age groups (87% of study participants). The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen.<sup>2</sup>

## Fosamprenavir (FPV, Lexiva)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations											
<p>Tablets: 700 mg</p> <p>Oral Suspension: 50 mg/mL</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>											
Dosing Recommendations	Selected Adverse Events										
<p><b>Pediatric Dose (Aged &gt;6 Months to 18 Years)</b></p> <ul style="list-style-type: none"> <li>Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but <b>not recommended</b> by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) because of low exposures (see text below).</li> <li>Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants <math>\geq 4</math> weeks and for treatment-experienced infants <math>\geq 6</math> months; however, the Panel <b>does not recommend</b> use in infants aged <math>&lt; 6</math> months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks' gestation or greater.</li> </ul> <p>Note: Once-daily dosing is <b>not recommended</b> for any pediatric patient.</p> <p><b>Pediatric Dose (Aged <math>\geq 6</math> Months to 18 Years)</b></p> <p>Twice-Daily Dose Regimens by Weight for Pediatric Patients <math>\geq 6</math> Months Using Fosamprenavir Oral Suspension with Ritonavir</p> <table border="1"> <thead> <tr> <th>Weight</th> <th>Dose (Both Drugs Twice Daily<sup>a</sup> with Food)</th> </tr> </thead> <tbody> <tr> <td>&lt;11 kg</td> <td>Fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose</td> </tr> <tr> <td>11 kg to &lt;15 kg</td> <td>Fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose</td> </tr> <tr> <td>15 kg to &lt;20 kg</td> <td>Fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose</td> </tr> <tr> <td><math>\geq 20</math> kg</td> <td>Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose</td> </tr> </tbody> </table>	Weight	Dose (Both Drugs Twice Daily <sup>a</sup> with Food)	<11 kg	Fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose	11 kg to <15 kg	Fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose	15 kg to <20 kg	Fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose	$\geq 20$ kg	Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose	<ul style="list-style-type: none"> <li>Diarrhea, nausea, vomiting</li> <li>Skin rash (fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)</li> <li>Headache</li> <li>Hyperlipidemia, hyperglycemia</li> <li>Nephrolithiasis</li> <li>Transaminase elevation</li> <li>Fat maldistribution</li> <li>Possible increased bleeding episodes in patients with hemophilia</li> </ul>
Weight	Dose (Both Drugs Twice Daily <sup>a</sup> with Food)										
<11 kg	Fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose										
11 kg to <15 kg	Fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose										
15 kg to <20 kg	Fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose										
$\geq 20$ kg	Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose										
	Special Instructions										
	<ul style="list-style-type: none"> <li>Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.</li> <li>Patients taking antacids should take fosamprenavir at least 1 hour before or after antacid use.</li> <li>Fosamprenavir contains a sulfonamide moiety. The potential for cross sensitivity between fosamprenavir and other drugs in the sulfonamide class is unknown. Fosamprenavir should be used with caution in patients with sulfonamide allergy.</li> <li>Shake oral suspension well before use. Refrigeration is not required.</li> </ul>										



<p><sup>a</sup> Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.</p> <p><b>Note:</b> When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing <math>\geq 39</math> kg. Ritonavir tablets can be used in patients weighing <math>\geq 33</math> kg.</p> <p><b>Adolescent and Adult Dose</b></p> <ul style="list-style-type: none"> <li>Dosing regimen depends on whether the patient is ARV-naive or ARV-experienced.</li> </ul> <p><i>ARV-Naive Patients</i></p> <ul style="list-style-type: none"> <li>Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily</li> <li>Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily</li> </ul> <p><i>Protease-Inhibitor-Experienced Patients</i></p> <ul style="list-style-type: none"> <li>Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.</li> </ul> <p><b>Note:</b> Once-daily administration of fosamprenavir plus ritonavir is <b>not recommended</b>.</p>	<table border="1"> <thead> <tr> <th data-bbox="821 191 1414 262">Metabolism/Elimination</th> </tr> </thead> <tbody> <tr> <td data-bbox="821 262 1414 451"> <ul style="list-style-type: none"> <li>The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.</li> <li>Amprenavir is a cytochrome P (CYP) 450 3A4 inhibitor, inducer, and substrate.</li> </ul> </td> </tr> <tr> <td data-bbox="821 451 1414 703"> <p><b>Fosamprenavir Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>Specific dose adjustments are recommended for adults with mild, moderate, and severe hepatic impairment. However, there are no data to support dosing recommendations for pediatric patients with hepatic impairment. Please refer to the <a href="#">package insert</a>.</li> </ul> </td> </tr> <tr> <td data-bbox="821 703 1414 972"> <p><b>Fosamprenavir Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required in patients with renal impairment.</li> </ul> </td> </tr> </tbody> </table>	Metabolism/Elimination	<ul style="list-style-type: none"> <li>The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.</li> <li>Amprenavir is a cytochrome P (CYP) 450 3A4 inhibitor, inducer, and substrate.</li> </ul>	<p><b>Fosamprenavir Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>Specific dose adjustments are recommended for adults with mild, moderate, and severe hepatic impairment. However, there are no data to support dosing recommendations for pediatric patients with hepatic impairment. Please refer to the <a href="#">package insert</a>.</li> </ul>	<p><b>Fosamprenavir Dosing in Patients with Renal Impairment</b></p> <ul style="list-style-type: none"> <li>No dose adjustment is required in patients with renal impairment.</li> </ul>
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## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Fosamprenavir may interact with a number of other drugs, and using ritonavir as a boosting agent increases the potential for drug interactions. Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

## Major Toxicities

- More common:* Vomiting, nausea, diarrhea, perioral paresthesia, headache, rash, lipid abnormalities
- Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.
- Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.
- Pediatric-specific:* Vomiting was more frequent in children than in adults during clinical trials of fosamprenavir with ritonavir (20% to 36% vs. 10%, respectively) and in trials of fosamprenavir without ritonavir (60% vs. 16%, respectively). Neutropenia was also more common in children across all the trials (15% vs. 3%, respectively).<sup>1</sup>

## Resistance

The International AIDS Society–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*

Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends use only in children aged  $\geq 6$  months. Although unboosted fosamprenavir has been approved by the FDA for antiretroviral-naïve children aged 2 to 5 years, the Panel **does not recommend** unboosted fosamprenavir for this—or any other—age group because of low exposures and also because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.<sup>2</sup>

## Efficacy and Pharmacokinetics

Dosing recommendations for fosamprenavir are based on three pediatric studies that enrolled more than 200 children aged 4 weeks to 18 years. In two, open-label trials in both treatment-experienced and treatment-naïve children aged 2 to 18 years,<sup>3,4</sup> fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of fosamprenavir/ritonavir in children; therefore, once-daily dosing **is not recommended** for pediatric patients.

### *Pharmacokinetics in Infants*

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naïve infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.<sup>1,5</sup> Exposures in those aged  $< 6$  months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir (see table below). Given these low exposures, limited data, large dosing volumes, unpleasant taste, and the availability of alternatives for infants and young children, the Panel **does not recommend** fosamprenavir use in infants aged  $< 6$  months.

**Table A. Fosamprenavir Dose and Amprenavir Exposure by Age Group**

Population	Dose	AUC <sub>0-24h</sub> (mcg*hr/mL) Except Where Noted	C <sub>min</sub> (mcg/mL)
Infants Aged <6 Months	FPV 45 mg/kg plus RTV 10 mg/kg twice daily	26.6 <sup>a</sup>	0.86
Children Aged 2 Years to <6 Years	FPV 30 mg/kg twice daily (no RTV)	22.3 <sup>a</sup>	0.513
Children Weighing <11 kg	FPV 45 mg/kg plus RTV 7 mg/kg twice daily	57.3	1.65
Children Weighing 15 kg to <20 kg	FPV 23 mg/kg FPV plus RTV 3 mg/kg twice daily	121.0	3.56
Children Weighing ≥20 kg	FPV 18 mg/kg plus RTV 3 mg/kg twice daily (maximum 700/100 mg)	72.3–97.9	1.98–2.54
Adults	FPV 1400 mg twice daily (no RTV)	33	0.35
Adults	FPV 1400 mg plus RTV 100–200 mg RTV once daily	66.4–69.4	0.86–1.45
Adults	FPV 700 mg plus RTV 100 mg twice daily	79.2	2.12

<sup>a</sup> AUC<sub>0-12</sub> (mcg\*hr/mL)

**Key:** AUC<sub>0-24h</sub> = area under the curve for 24 hours post-dose; C<sub>min</sub> = minimum plasma concentration; FPV = fosamprenavir; RTV = ritonavir

**Note:** Dose for those weighing 11 kg to <15 kg is based on population pharmacokinetic studies; therefore, AUC and C<sub>min</sub> are not available.

## Indinavir (IDV, Crixivan)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations		
<p>Capsules: 100 mg, 200 mg, and 400 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>		
Dosing Recommendations	Selected Adverse Events	
<p><b>Neonate and Infant Dose</b></p> <ul style="list-style-type: none"> <li>Not approved for use in neonates/infants</li> <li>Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus)</li> </ul> <p><b>Pediatric Dose</b></p> <ul style="list-style-type: none"> <li>Not approved for use in children</li> <li>A range of indinavir doses (234–500 mg/m<sup>2</sup> body surface area) boosted with low-dose ritonavir has been studied in children (see text below).</li> </ul> <p><b>Adolescent and Adult Dose</b></p> <ul style="list-style-type: none"> <li>800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours</li> <li>The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV <b>does not recommend</b> the use of indinavir in adolescents.</li> </ul>	<ul style="list-style-type: none"> <li>Nephrolithiasis</li> <li>Gastrointestinal intolerance, nausea</li> <li>Hepatitis</li> <li>Indirect hyperbilirubinemia</li> <li>Hyperlipidemia</li> <li>Hyperglycemia</li> <li>Fat maldistribution</li> <li>Possible increased bleeding episodes in patients with hemophilia</li> </ul>	
		Special Instructions
		<ul style="list-style-type: none"> <li>When indinavir is given in combination with ritonavir, meal restrictions are not necessary.</li> <li>Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).</li> <li>Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.</li> </ul>
		Metabolism/Elimination
	<ul style="list-style-type: none"> <li>Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate</li> </ul> <p><b>Indinavir Dosing in Patients with Hepatic Impairment</b></p> <ul style="list-style-type: none"> <li>Dose should be decreased in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.</li> </ul>	

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Metabolism:* Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions with indinavir.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

## Major Toxicities

- *More common:* Nephrolithiasis/urolithiasis with indinavir crystal deposit is reported more frequently in children (29%) than in adults (12.4%).<sup>1</sup> Interstitial nephritis and urothelial inflammation has been commonly reported in adults.<sup>2</sup> Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash.
- *Less common (more severe):* Fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).

## Resistance

The International AIDS Society–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*

Indinavir has not been approved by the Food and Drug Administration for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.<sup>3</sup> Indinavir **is not recommended** by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV for use in children and adolescents because of its unfavorable toxicity profile, limited efficacy data, and uncertain pharmacokinetics.

### *Efficacy and Pharmacokinetics*

Both unboosted and ritonavir-boosted indinavir have been studied in children with HIV. In children, an unboosted indinavir dose of 500 to 600 mg/m<sup>2</sup> body surface area given every 8 hours results in peak blood concentrations and area under the curve that are slightly higher than those in adults, but trough concentrations are considerably lower. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.<sup>4-7</sup>

Studies that investigated a range of indinavir/ritonavir doses in small groups of children have shown that indinavir 500 mg/m<sup>2</sup> body surface area plus ritonavir 100 mg/m<sup>2</sup> body surface area twice daily is probably too high,<sup>8</sup> that indinavir 234 to 250 mg/m<sup>2</sup> body surface area plus low-dose ritonavir twice daily is too low,<sup>9,10</sup> and that indinavir 400 mg/m<sup>2</sup> body surface area plus ritonavir 100 to 125 mg/m<sup>2</sup> body surface area twice daily results in exposures approximating those seen with indinavir 800 mg plus ritonavir 100 mg twice daily in adults, albeit with considerable inter-individual variability and high rates of toxicity.<sup>10-12</sup>

## Nelfinavir (NFV, Viracept)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations		
Tablets: 250 mg and 625 mg		
For additional information, see <a href="#">Drugs@FDA</a> .		
Dosing Recommendations	Selected Adverse Events	
<p><b>Note:</b> The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV <b>no longer recommends</b> nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.</p> <p><b>Neonate and Infant Dose</b></p> <ul style="list-style-type: none"> <li>Nelfinavir should not be used for treatment in children aged &lt;2 years.</li> </ul> <p><b>Pediatric Dose (Aged ≥2 Years)</b></p> <ul style="list-style-type: none"> <li>45–55 mg/kg twice daily</li> </ul> <p><b>Adolescent and Adult Dose</b></p> <ul style="list-style-type: none"> <li>1,250 mg (five 250-mg tablets or two 625-mg tablets) twice daily</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea</li> <li>Hyperlipidemia</li> <li>Hyperglycemia</li> <li>Fat maldistribution</li> <li>Serum transaminase elevations</li> </ul>	
		Special Instructions
		<ul style="list-style-type: none"> <li>Administer nelfinavir with meal or light snack.</li> <li>If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.</li> <li>Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.</li> </ul>
		Metabolism/Elimination
	<ul style="list-style-type: none"> <li>Cytochrome P (CYP) 2C19 and 3A4 substrate</li> <li>Metabolized to active M8 metabolite</li> <li>CYP3A4 inhibitor</li> </ul>	

### Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Metabolism:** Cytochrome P (CYP) 2C19 and 3A4 substrate and CYP3A4 inhibitor. Ritonavir boosting does not significantly increase nelfinavir concentrations, and co-administration of nelfinavir with ritonavir **is not recommended**.



- There is potential for multiple drug interactions with nelfinavir. Before administering nelfinavir, carefully review a patient’s medication profile for potential drug interactions.

## Major Toxicities

- *More common:* Diarrhea (most common), asthenia, abdominal pain, rash, lipid abnormalities
- *Less common (more severe):* Fat redistribution, exacerbation of chronic liver disease
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, elevations in transaminases

## Resistance

The International AIDS Society–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*

Nelfinavir is approved by the Food and Drug Administration (FDA) for use in children aged  $\geq 2$  years. Given the higher variability of nelfinavir plasma concentrations in infants and younger children,<sup>1,2</sup> nelfinavir is not approved for children aged  $< 2$  years. Despite being FDA-approved for pediatric use, nelfinavir **is not recommended** for use in children and adolescents by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, due to its limited efficacy and uncertain pharmacokinetics (PK).

### *Efficacy in Pediatric Clinical Trials*

Nelfinavir used in combination with other antiretroviral (ARV) drugs has been extensively studied in children with HIV infection.<sup>3-10</sup> In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple combination therapy, the proportion of patients with HIV RNA  $< 400$  copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. The antiviral response to nelfinavir is significantly less in children aged  $< 2$  years than in older children.<sup>8,10,11</sup> In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient’s age or prior treatment history, the number of drugs included in the combination regimen, and the dose of nelfinavir used.

### *Pharmacokinetics: Exposure-Response Relationships*

Nelfinavir’s relatively poor ability to control plasma viremia in infants and children in clinical trials may be related to its lower potency when compared with other ARV drugs, as well as highly variable drug exposure, metabolism, and poor palatability.<sup>12-14</sup> The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.<sup>3,15</sup>

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increases by up to fivefold) and decreases PK variability when compared to the fasted state. Nelfinavir plasma exposure may be even more unpredictable in pediatric patients than in adults due to the increased

clearance of nelfinavir observed in children and difficulties in taking nelfinavir with sufficient food to improve bioavailability.

Nelfinavir is metabolized by multiple CYP450 enzymes, including CYP3A4 and CYP2C19. The variability of drug exposure at any given dose is much higher for children than for adults,<sup>16</sup> which has been attributed—at least in part—to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children.<sup>17,18</sup> Furthermore, CYP2C19 genotype has been shown to affect nelfinavir PK and the virologic responses in children with HIV.<sup>12</sup>

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults, an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration ( $C_{min}$ ) <1.0 mcg/mL.<sup>19-21</sup>

In a study of 32 children treated with a high dose of nelfinavir (a twofold increase of the recommended dose), 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had HIV RNA concentrations <50 copies/mL at Week 48, compared with only 29% of those with morning trough <0.8 mcg/mL.<sup>22</sup> Children in the group with  $C_{trough}$  <0.8 mcg/mL were younger than the children in the group with  $C_{trough}$  >0.8 mcg/mL (median ages in these groups were 3.8 years and 8.3 years, respectively).<sup>22</sup> Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, has been shown to improve virologic response in adults and children.<sup>18,19,23,24</sup> Pediatric and adolescent patients may require doses higher than those recommended in adults to achieve higher plasma nelfinavir exposure.

## Saquinavir (SQV, Invirase)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations	
Capsules: 200 mg Tablets: 500 mg For additional information, see <a href="#">Drugs@FDA</a> .	
Dosing Recommendations	Selected Adverse Events
<b>Pediatric Dose</b> <ul style="list-style-type: none"> <li>Not approved for use in infants, children, and adolescents aged &lt;16 years.</li> </ul> <b>Adolescent and Adult Dose</b> <ul style="list-style-type: none"> <li>Saquinavir should <b>only</b> be used in combination with ritonavir.</li> <li>Saquinavir 1000 mg plus ritonavir 100 mg twice daily</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal intolerance, nausea, diarrhea</li> <li>Elevated transaminases</li> <li>Hyperlipidemia</li> <li>Hyperglycemia</li> <li>Fat maldistribution</li> <li>PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>Administer within 2 hours after a full meal.</li> <li>Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.</li> <li>Pre-therapy electrocardiogram is recommended; saquinavir is <b>contraindicated</b> in patients with a prolonged QT interval.</li> </ul>
	Metabolism/Elimination
	<ul style="list-style-type: none"> <li>Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor</li> <li>90% metabolized in the liver</li> <li>Use saquinavir with caution in patients who have hepatic impairment; no dose adjustment recommended.</li> </ul>

### Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Saquinavir is both a substrate and inhibitor of the cytochrome P 450 3A4 (CYP3A4) system. Potential exists for multiple drug interactions. Saquinavir **should not be coadministered** with

drugs that are highly dependent on CYP3A clearance, especially in cases where elevated plasma concentrations of the coadministered drug can cause serious or life-threatening events.

- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

## Major Toxicities

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, lipid abnormalities
- *Less common (more severe):* Exacerbation of chronic liver disease, lipodystrophy
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, pancreatitis, and elevation in serum transaminases. Saquinavir administered with ritonavir can lead to prolonged QT and/or PR intervals with potential for heart block and ventricular tachycardia (Torsades de Pointes).

## Resistance

The International AIDS Society–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*

Saquinavir is not approved for use in children or adolescents aged <16 years.<sup>1</sup>

### *Efficacy*

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors and other protease inhibitors in children with HIV.<sup>2-9</sup> Saquinavir/ritonavir (SQV/r) and a dual-protease inhibitor saquinavir/lopinavir/ritonavir regimen were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications; these regimens **are no longer recommended**.

### *Pharmacokinetics*

Pharmacokinetic (PK) data from children who received SQV/r showed prohibitively low exposure in children younger than 2 years.<sup>10</sup> In children aged  $\geq 2$  years, a dose of saquinavir 50 mg/kg twice daily in combination with ritonavir and lopinavir/ritonavir resulted in steady-state plasma trough concentrations ( $C_{\text{trough}}$ ) similar to those seen adults.<sup>9,11</sup> No clinical trials have collected data on the efficacy of saquinavir doses <50 mg/kg in children.

### *Toxicity*

In healthy adult volunteers, SQV/r dose and exposure were associated with increases in both QT and PR intervals.<sup>1,12</sup> Rare cases of Torsades de Pointes and complete heart block have been reported in postmarketing surveillance. SQV/r **is not recommended** for adolescent and adult patients with any

of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete atrioventricular block, or the use of other drugs that prolong QT interval. An electrocardiogram (EKG) is recommended before initiation of therapy with saquinavir and repeat EKGs should be considered during therapy.

Steady-state saquinavir exposures observed in one pediatric trial (NV20911) were substantially higher than those seen in historical data from adults with QT and PR prolongation.<sup>1,12</sup> Although no EKG abnormalities have been reported among the small number of subjects in pediatric trials, pediatric PK/pharmacodynamics modeling suggests that reducing the saquinavir dose in order to minimize the risk of QT prolongation would decrease saquinavir efficacy in children. Pediatric saquinavir dose recommendations that were both reliably effective and below the thresholds of concern for QT and PR prolongation were not determined.

## Stavudine (d4T, Zerit)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations	
<p><b>Powder for Oral Solution:</b> 1 mg/mL</p> <p><b>Capsules:</b> 15 mg, 20 mg, 30 mg, and 40 mg</p> <p><b>Generic Formulations</b></p> <p><b>Powder for Oral Solution:</b> 1 mg/mL</p> <p><b>Capsules:</b> 15 mg, 20 mg, 30 mg, and 40 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Note:</b> Stavudine is no longer recommended for use in children by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, because it causes higher rates of adverse effects than other nucleoside reverse transcriptase inhibitors (NRTIs).</p> <p><b>Pediatric (Aged <math>\geq 14</math> Days and Weighing <math>&lt; 30</math> kg) Dose</b></p> <ul style="list-style-type: none"> <li>1 mg/kg per dose twice daily</li> </ul> <p><b>Adolescent (Weighing <math>\geq 30</math> kg) and Adult Dose</b></p> <ul style="list-style-type: none"> <li>30 mg per dose twice daily</li> </ul>	<ul style="list-style-type: none"> <li>Associated with a higher risk of mitochondrial toxicity than other NRTI drugs</li> <li>Peripheral neuropathy is dose-related and occurs more frequently in patients who have advanced HIV disease or a prior history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy.</li> <li>Facial/peripheral lipoatrophy</li> <li>Pancreatitis</li> <li>Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other NRTIs). The risk increases when stavudine is used in combination with didanosine.</li> <li>Dyslipidemia</li> <li>Insulin resistance, asymptomatic hyperglycemia</li> <li>Rapidly progressive ascending neuromuscular weakness (rare)</li> </ul>
	Special Instructions
	<ul style="list-style-type: none"> <li>Stavudine can be given without regard to food.</li> <li>Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.</li> </ul>
	Metabolism/Elimination
	<ul style="list-style-type: none"> <li>Renal excretion 50%. Decrease dose in patients with renal dysfunction.</li> <li>Stavudine is phosphorylated intracellularly to the active metabolite stavudine triphosphate.</li> </ul>

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Stavudine **should not be administered** in combination with zidovudine because of virologic antagonism.
- *Overlapping toxicities:* The combination of stavudine and didanosine **is not recommended** because of overlapping toxicities. Reported toxicities occur more frequently in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.
- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in patients with HIV/hepatitis C virus co-infection who are receiving antiretroviral therapy (ART), interferon, and ribavirin.
- *Doxorubicin:* Simultaneous use of doxorubicin and stavudine should be avoided. Doxorubicin may inhibit the phosphorylation of stavudine to its active form.

## Major Toxicities

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, fat maldistribution
- *Less common (more severe):* Peripheral sensory neuropathy is dose-related. It occurs more frequently in patients with advanced HIV disease, a prior history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy. Pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported.<sup>1-3</sup> The combination of stavudine and didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant persons—**this combination should not be used**. Risk factors found to be associated with lactic acidosis in adults include female sex, obesity, and prolonged nucleoside exposure.<sup>4</sup>
- *Rare:* Increased liver enzymes and hepatic toxicity, which may be severe or fatal. Neurologic symptoms, including rapidly progressive ascending neuromuscular weakness, are most often seen in the setting of lactic acidosis. Noncirrhotic portal hypertension with prolonged exposure.

## Resistance

The International AIDS Society–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*

Although stavudine is Food and Drug Administration (FDA)-approved for use in infants aged  $\geq 14$  days and children, it **is no longer recommended** for use by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV because it carries a higher risk of adverse effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

### *Efficacy*

Data from multiple pediatric studies of stavudine administered alone or in combination with other antiretroviral (ARV) agents demonstrate that stavudine is associated with clinical and virologic response.<sup>5-11</sup> In resource-limited countries, stavudine is frequently a component of initial ART in children, given with lamivudine and nevirapine. Stavudine is often a component of fixed-dose combinations that are not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte (CD4) cell count and complete viral suppression in 50% to 80% of treatment-naïve children.<sup>12-15</sup> In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.<sup>16</sup> Short-term use of stavudine in certain settings where access to other ARVs may be limited remains an important strategy for treating HIV in children.<sup>17,18</sup>

### *Toxicity*

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.<sup>19,20</sup> In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest—but significantly higher—rate of clinical and laboratory toxicities than regimens containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.<sup>20</sup>

### *Lipodystrophy and Metabolic Abnormalities*

Lipodystrophy syndrome (LS), and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.<sup>21-24</sup> Stavudine use has consistently been associated with a higher risk of lipodystrophy and other metabolic abnormalities (e.g., insulin resistance) in multiple pediatric studies involving children.<sup>25-33</sup> Improvements in (or resolution of) lipodystrophy were reported in 22.9% to 73% of cases after discontinuation of stavudine in two separate studies.<sup>30,34</sup>

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.<sup>1-3</sup>

### *Mechanism*

Many of the stavudine-related adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial

DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues.<sup>1,35-37</sup> In a recent analysis involving a large cohort of pediatric patients (PACTG protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.<sup>38</sup>

### ***World Health Organization Recommendations***

The World Health Organization (WHO) cautions against using doses of stavudine that exceed 30 mg twice daily. This is in contrast to the FDA-recommended dose of 40 mg twice daily in patients weighing 60 kg or more.<sup>39,40</sup> Studies comparing the efficacy and toxicity of the two doses have consistently shown that both doses have similar efficacy. However, while the 30-mg dose shows lower toxicity than the 40-mg dose, the overall incidence of toxicity with the 30-mg dose is considered to be unacceptably high.<sup>41-45</sup> WHO recommends that stavudine be phased out of use in all patients because of concerns about unacceptable toxicity, even at the lower dose. Safer alternative agents can be prescribed.

### **Pharmacokinetics**

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.<sup>46</sup> Although WHO has recommended using a reduced dose in adults, a similar dose reduction has not been suggested in children. A reduced pediatric dose has been proposed based on PK modeling, but clinical data on intracellular concentrations of the active stavudine triphosphate are lacking.<sup>47,48</sup> Intracellular stavudine triphosphate concentrations have not been measured in neonates.

### **Formulations**

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, with the appropriate dose drawn up into an oral syringe and administered immediately. Because plasma exposure of stavudine is equivalent whether the drug is administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.<sup>49</sup>

## Tipranavir (TPV, Aptivus)

Updated: May 22, 2018

Reviewed: May 22, 2018

Formulations	
<p><b>Oral Solution:</b> 100 mg tipranavir/mL with 116 International Units (IU) vitamin E/mL</p> <p><b>Capsules:</b> 250 mg</p> <p>For additional information, see <a href="#">Drugs@FDA</a>.</p>	
Dosing Recommendations	Selected Adverse Events
<p><b>Note:</b> Tipranavir must be boosted with ritonavir. The ritonavir boosting dose used for tipranavir is higher than the doses used for other protease inhibitors.</p> <p><b>Pediatric (Aged &lt;2 Years) Dose</b></p> <ul style="list-style-type: none"> <li>Not approved for use in children aged &lt;2 years</li> </ul> <p><b>Pediatric (Aged 2–18 Years) Dose</b></p> <p><b>Note:</b> Not recommended for treatment-naïve patients</p> <p><i>Body Surface Area Dosing</i></p> <ul style="list-style-type: none"> <li>Tipranavir/ritonavir (TPV/r) 375 mg/m<sup>2</sup>/150 mg/m<sup>2</sup>, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)</li> </ul> <p><i>Weight-Based Dosing</i></p> <ul style="list-style-type: none"> <li>TPV/r 14 mg/kg/6 mg/kg, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)</li> </ul> <p><b>Adult Dose</b></p> <ul style="list-style-type: none"> <li>TPV/r 500 mg (as two 250-mg capsules)/200 mg, both twice daily</li> </ul> <p><b>Note:</b> Not recommended for treatment-naïve patients</p>	<ul style="list-style-type: none"> <li>Rare cases of fatal and nonfatal intracranial hemorrhage</li> <li>Skin rash (more common in children than adults)</li> <li>Nausea, vomiting, diarrhea</li> <li>Hepatotoxicity: elevated transaminases; clinical hepatitis</li> <li>Hyperlipidemia</li> <li>Hyperglycemia</li> <li>Elevated creatine phosphokinase</li> </ul>
	<ul style="list-style-type: none"> <li>Administer tipranavir and ritonavir together and with food.</li> <li>Tipranavir oral solution contains 116 IU vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.</li> <li>Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.</li> <li>Store tipranavir oral solution at room temperature, 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.</li> <li>Store unopened bottles of oral tipranavir capsules in a refrigerator at 2°C to 8°C (36°F to 46°F). Once the bottle has been opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.</li> <li>Use tipranavir with caution in patients who may be at increased risk of intracranial hemorrhage, including individuals with brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcoholism, or who use anticoagulant or antiplatelet agents (including vitamin E).</li> <li>Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.</li> </ul>

	Metabolism/Elimination
	<ul style="list-style-type: none"> <li>• Cytochrome P450 3A4 (CYP3A4) inducer and substrate</li> <li>• P-glycoprotein substrate</li> </ul> <p>Tipranavir Dosing in Patients with Renal Impairment</p> <ul style="list-style-type: none"> <li>• No dose adjustment is required.</li> </ul> <p>Tipranavir Dosing in Patients with Hepatic Impairment</p> <ul style="list-style-type: none"> <li>• No dose adjustment is required for mild hepatic impairment.</li> <li>• Use of tipranavir is <b>contraindicated</b> in patients with moderate-to-severe hepatic impairment.</li> </ul>

## Drug Interactions

Additional information about drug interactions is available in the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#).

- Tipranavir has the potential for multiple drug interactions. Co-administration of tipranavir/ritonavir (TPV/r) with drugs that are highly dependent on cytochrome P (CYP) 3A for clearance or are potent CYP3A inducers is contraindicated.
- Before tipranavir is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions.
- TPV/r is a potent enzyme inducer and has the potential to decrease plasma concentrations of other antiretroviral drugs. TPV/r significantly decreases plasma concentrations of etravirine. Etravirine and TPV/r **should not be co-administered**.
- TPV/r has been shown to decrease raltegravir concentrations. TPV/r dose adjustment **is not currently recommended** when raltegravir is administered twice daily. However, TPV/r **should not be co-administered** with raltegravir HD once daily because significantly lower raltegravir concentrations are likely to occur.
- Tipranavir should be used with caution in patients who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

## Major Toxicities

- *More common:* Diarrhea, nausea, fatigue, headache, rash (which is more frequent in children than in adults), and vomiting. Elevated transaminases, cholesterol, and triglycerides. Elevated creatine phosphokinase.
- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis, which is more common with oral solution than capsule formulation.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage. Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

## Resistance

The International AIDS Society–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 and General Considerations*

Tipranavir is approved for use in children aged as young as 2 years and is available in a liquid formulation.

Its indication is limited to those patients who are treatment-experienced and who have HIV strains that are resistant to more than one protease inhibitor (PI).<sup>1</sup> Tipranavir imposes a high pill burden on patients taking tipranavir capsules and requires a higher dose of boosting ritonavir than the doses used with other PIs. This increased dose of ritonavir is associated with a greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events (AEs) that limit its use to patients with few treatment options.

## Efficacy

The Food and Drug Administration's approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of TPV/r in children with HIV (PACTG 1051/BI-1182.14).<sup>2</sup> This study enrolled 110 treatment-experienced children (with the exception of three treatment-naïve patients) aged 2 years to 18 years (with a median age of 11.7 years). Patients were randomized to receive two different dosing regimens. The higher dose of TPV/r (375 mg/150 mg/m<sup>2</sup> body surface area [BSA] twice daily) plus optimized background therapy was associated with better virologic responses at 48 weeks, particularly in the older, more heavily pretreated patients, when compared to the lower dose that was studied. A follow-up study of PACTG 1051 participants evaluated the long-term safety, efficacy, and tolerability of TPV/r in pediatric patients.<sup>3</sup> At Week 288, most children were no longer receiving TPV/r. Reasons for discontinuation included AEs, virologic failure, and nonadherence. The youngest patients who were stable at Week 48 were more likely to still be on treatment after 5 years with continued efficacy.<sup>3</sup>

## Pharmacokinetics

PK evaluation of the liquid formulation at steady state in children was assessed.<sup>4</sup> In children aged 2 to <12 years, a dose of TPV/r 290 mg/115 mg/m<sup>2</sup> BSA achieved tipranavir trough concentrations that were consistent with those achieved in adults receiving standard TPV/r 500 mg/200 mg dosing. However, children aged 12 to 18 years required a higher dose (375 mg/150 mg/m<sup>2</sup> BSA, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that seen in adults receiving the standard TPV/r dose. Based on available data, a dose of TPV/r 375 mg/150 mg/m<sup>2</sup> BSA twice daily is recommended.

## Toxicity

AEs were similar between treatment groups in the multicenter, pediatric study.<sup>2</sup> Twenty-five percent of children experienced a drug-related serious AE, and 9% of patients discontinued study drugs because of AEs. The most common AEs were gastrointestinal disturbances: 37% of participants had vomiting and 24% had diarrhea. The most common Grade 3 through 4 laboratory abnormalities were increases in the levels of creatine phosphokinase (11% of participants), alanine aminotransferase (6.5% of participants), and amylase (7.5% of participants). In the long-term follow-up report for PACTG 1051, incidence of AEs defined as drug-related was 55% to 65% regardless of age at entry, with higher discontinuation rates due to AEs in the older age groups.<sup>3</sup>

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 international units (IU) of vitamin E and 100 mg tipranavir per mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/kg body weight per day, significantly higher than the reference daily intake for vitamin E (which is 30 IU for adults and approximately 6–22 IU for children and adolescents, depending on age of the child or adolescent) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%).<sup>2</sup> Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.<sup>5</sup>