



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

## Appendix A: Pediatric Antiretroviral Drug Information

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### **Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors**

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

## Abacavir (ABC, Ziagen) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Pediatric Oral Solution:** 20 mg/mL

**Tablet:** 300 mg (scored)

#### Generic Formulations:

- 300 mg tablet
- 20 mg/mL pediatric oral solution

#### Fixed-Dose Combination Tablets:

- [Epzicom and generic] Abacavir 600 mg/lamivudine 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

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

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

### Dosing Recommendations

#### Neonate (Aged <1 Month):

- Abacavir (ABC) is not approved by the Food and Drug Administration (FDA) for use in neonates aged <3 months.

#### Infant (Aged ≥1 Month to <3 Months) Dose

*Oral Solution:*

- **Recent data from the IMPAACT P1106 trial and two observational cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age (see Approval section below). Based on these data, The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends ABC 8 mg/kg twice daily in full-term infants ≥1 month to <3 months of age.**

#### Infant and Child (Aged ≥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. In older children who can be treated with tablet formulations, therapy can be initiated with once-daily administration. In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts while receiving the liquid formulation of ABC twice daily, the ABC dose can be changed from twice-daily dosing to once-daily dosing with the liquid or tablet formulations (see text below).

### Selected Adverse Events

- 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).

### Special Instructions

- 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 ABC. Patients with no prior HLA-B\*5701 testing who are tolerating ABC do not need to be tested.
- Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of ABC. Do not rechallenge.**
- ABC can be given without regard to food. The oral solution does not require refrigeration.
- Screen patients for hepatitis B virus (HBV) infection before using ABC fixed-dose combination (FDC) tablets that contain lamivudine (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.

## Weight-Band Dosing for Children and Adolescents Weighing $\geq 14$ kg

Weight	Scored 300-mg 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)
$\geq 25$ kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 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] 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 antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The Food and Drug Administration-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg (see the [Dolutegravir](#) section for more information).

#### [Trizivir] Abacavir/Lamivudine/Zidovudine

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

- One tablet twice daily

- The majority of ABC is excreted as metabolites in urine.

### Abacavir Dosing in Patients with Hepatic Impairment:

- ABC requires a dose adjustment in patients **mild** hepatic insufficiency **and is contraindicated with moderate or severe hepatic insufficiency.**
- **Do not use** Trizivir, Epzicom, and 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:

- Abacavir does not require dose adjustment in patients with renal impairment.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets) in patients with creatinine clearance <50 mL/min and patients on dialysis, because the doses of 3TC (in all three FDCs) **and ZDV** (in Trizivir and generic) cannot be adjusted.

# Emtricitabine (FTC, Emtriva)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Pediatric Oral Solution:** 10 mg/mL

**Capsule:** 200 mg

### Fixed-Dose Combination Tablets:

- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Descovy] Emtricitabine 200 mg/tenofovir alafenamide 25 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Truvada] Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada low-strength tablets]
  - Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg
  - Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg
  - Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg

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

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

## Dosing Recommendations

### Neonatal and Infant (Aged 0 to <3 Months) Dose

*Oral Solution:*

- Emtricitabine (FTC) 3 mg/kg once daily

### Child (Aged ≥3 Months) and Adolescent Dose

*Oral Solution:*

- 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.

*Capsules (For Patients Weighing >33 kg):*

- FTC 200 mg once daily

### Adult Dose

*Oral Solution for Patients Who Are Unable to Swallow Capsules:*

- FTC 240 mg (24 mL) once daily

*Capsules:*

- FTC 200 mg once daily

## Selected Adverse Events

- Hyperpigmentation/skin discoloration on palms and/or soles

## Special Instructions

- Although FTC can be administered without regard to food, there are food requirements for some FDC tablet formulations that contain FTC.
- 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.
- 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.

### **[Atripla and Generic] Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)**

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

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

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

*Child (Weighing  $< 25$  kg) Dose:*

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

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

- One tablet once daily, with or without food. Food and Drug Administration guidance suggests 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. However, many panel members would use Biktarvy in patients with prior treatment failure who have the virus containing the M184V mutation.
- See the [Bictegravir](#) section for additional information.

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

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

- One tablet once daily in ART-naïve patients who have baseline plasma HIV RNA  $\leq 100,000$  copies/mL. This dose of Complera can also 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) for at least 6 months 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] Emtricitabine/TAF**

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

## **Metabolism/Elimination**

- No cytochrome P450 interactions
- Eighty-six percent of FTC is excreted in urine. FTC may compete with other compounds that undergo renal elimination.

### **Emtricitabine Dosing in Patients with Hepatic Impairment:**

- Atripla should be used with caution in patients with hepatic impairment.
- Biktarvy, Genvoya, Stribild, and Symtuza are not recommended for use in patients with severe hepatic impairment.
- 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.

### **Emtricitabine Dosing in Patients with Renal Impairment:**

- Decrease the dose of FTC in patients with impaired renal function. Consult the manufacturer's prescribing information for recommended dose adjustments.
- **Do not use** the FDC tablet Atripla **or Complera** in patients with creatinine clearance (CrCl)  $< 50$  mL/min or in patients who require dialysis.
- **Do not use** the FDC tablets Truvada or Biktarvy in patients with CrCl  $< 30$  mL/min. Do not use Truvada in patients who require dialysis.
- 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.

Body Weight 25 kg to <35 kg:

- One tablet once daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., in this weight band, Descovy can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).

Body Weight ≥35 kg:

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

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

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

- One tablet once daily with food in ART-naive patients. This dose of Genvoya can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

**[Odefsey] Emtricitabine/Rilpivirine/TAF**

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

- One tablet once daily in ART-naive patients with HIV RNA ≤100,000 copies per 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/Cobicistat/Emtricitabine/TDF**

*Child and Adolescent (Weighing ≥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 can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <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 Stribild.

**[Symtuza] Darunavir/Cobicistat/Emtricitabine/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) for at least 6 months with no known mutations associated with resistance to darunavir or tenofovir.

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

*Child, Adolescent, and Adult Dose:*

**Truvada Dosing Table**

<b>Body Weight</b>	<b>FTC/TDF Tablet Once Daily</b>
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



## Lamivudine (3TC, Epivir) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

#### Pediatric Oral Solution:

- [Epivir] 10 mg/mL
- [Epivir HBV]<sup>a</sup> 5 mg/mL

#### Tablets:

- [Epivir] 150 mg (scored) and 300 mg
- [Epivir HBV]<sup>a</sup> 100 mg

#### Generic Formulations:

- 100-mg, 150 mg, and 300 mg tablets
- Fixed-dose combination (FDC) tablet containing lamivudine 150 mg/zidovudine 300 mg

#### Fixed-Dose Combination Tablets:

- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Epzicom] Abacavir 600 mg/lamivudine 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

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

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

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Table 12: Antiretroviral Dosing Recommendations for Newborns](#) for information about using lamivudine (3TC) for the prevention of perinatal HIV transmission.

#### Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to <4 Weeks) Dose

##### Oral Solution:

- 3TC 2 mg/kg twice daily

##### Infant and Child Dose:

- Once-daily dosing of the 3TC oral solution **is not recommended** when initiating 3TC oral solution in infants and young children. Patients can be transitioned to once-daily

### Selected Adverse Events

- **Headache**

### Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for hepatitis B virus (HBV) infection before using 3TC or FDC tablets that contain 3TC. Severe acute exacerbations of hepatitis B can occur after discontinuation of lamivudine. Hepatic function and hepatitis B 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.

treatment with the oral solution when they have been stable on twice-daily treatment for 36 weeks and are aged  $\geq 3$  years. Please see the note below and refer to the text for more detail.

*Aged  $\geq 4$  Weeks to  $< 3$  Months:*

- 3TC 4 mg/kg twice daily of the oral solution

*Aged  $\geq 3$  Months to  $< 3$  Years:*

- 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)

*Aged  $\geq 3$  Years:*

- 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose); *or*
- 3TC 10 mg/kg once daily of the oral solution (maximum 300 mg per dose)

**Weight-Band Dosing for the 10 mg/mL Lamivudine Oral Solution in Children Weighing  $\geq 3$  kg**

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM
3 kg-5.9 kg	3 ml	3 ml
6 kg-9.9 kg	4 ml	4 ml
10 kg-3.9 kg	6 ml	6 ml

*Weighing  $\geq 14$  kg and Able to Swallow Tablets:*

- Weight-band dosing (see table below; dose is approximately 3TC 5 mg/kg per day twice daily or 3TC 10 mg/kg once daily)
- The scored tablet is the preferred formulation for pediatric patients weighing  $\geq 14$  kg who can swallow a tablet.

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

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to $< 20$ kg	$\frac{1}{2}$ tablet (75 mg)	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)
$\geq 20$ kg to $< 25$ kg	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)	$1\frac{1}{2}$ 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

## Metabolism/Elimination

### Lamivudine Dosing in Patients with Hepatic Impairment:

- No change in 3TC dosing is required for patients with hepatic impairment.
- FDC tablets containing abacavir (ABC) or zidovudine (ZDV) should not be used in patients who have impaired hepatic function.
- Symfi and Symfi Lo should be used in 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.

### Lamivudine Dosing in Patients with Renal Impairment:

- Dose adjustment is required for patients with renal insufficiency.
- FDC tablets should not be used in patients who are on dialysis, patients who have creatinine clearance  $< 50$  mL/min, or patients who have impaired hepatic function.

who have been clinically stable for 36 weeks with undetectable viral loads and stable CD4 T lymphocyte 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] Lamivudine/Tenofovir Disoproxil Fumarate (TDF)**

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

- One tablet once daily

**[Combivir and Generic] Lamivudine/Zidovudine**

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

- One tablet twice daily

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

*Adult Dose:*

- One tablet once daily
- The use of Delstrigo has not been studied in children or adolescents (see the [Doravirine](#) section for more information).

**[Dovato] Dolutegravir/Lamivudine**

*Adult Dose:*

- One tablet once daily with or without food as a complete antiretroviral (ARV) regimen in antiretroviral therapy (ART)-naive adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the 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] Abacavir/Lamivudine**

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

- One tablet once daily

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

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

- One tablet once daily on an empty stomach

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

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

- One tablet once daily

**[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 ART-naive or ART-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg (see the [Dolutegravir](#) section for more information).

**[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine**

*Child and Adolescent (Weighing  $\geq 30$  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.

# Tenofovir Alafenamide (TAF, Vemlidy)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Tablets:** 25 mg<sup>a</sup>

### Fixed-Dose Combination Tablets:

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

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

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

## Dosing Recommendations

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

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

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

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

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

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

- One tablet once daily, with or without food. **The Food and Drug Administration approved Biktarvy for use** in antiretroviral therapy-naïve patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy. **Some members on**

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

## Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before initiating TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TAF.
- The Food and Drug Administration (FDA) does not recommend using Genvoya with other ARV drugs, but this FDC tablet has safely been used with darunavir (DRV).<sup>1</sup> Descovy can be safely used with DRV or atazanavir in patients weighing ≥35 kg.<sup>2</sup>
- **Do not use** Genvoya with elvitegravir, cobicistat (COBI), tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated with COBI.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal) because it contains rilpivirine.

## Metabolism/Elimination

### TAF Dosing in Patients with Hepatic Impairment:

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

the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) would use Biktarvy in patients with prior treatment failure who have virus with the M184V mutation. See the [Bictegravir](#) section for additional information.

### [Descovy] Emtricitabine/TAF

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

Body Weight 25 kg to  $< 35$  kg:

- One tablet once daily in combination with an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). **In this weight band** Descovy should not be used with protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., ritonavir or cobicistat).

Body Weight  $\geq 35$  kg:

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

### [Genvoya]

#### Elvitegravir/Cobicistat/Emtricitabine/TAF

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

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

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

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

### [Odefsey] Emtricitabine/Rilpivirine/TAF

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

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

moderate hepatic impairment, but they should not be used in patients with severe hepatic impairment because they have not been studied in that group.

### TAF Dosing in Patients with Renal Impairment:

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

patients with HIV RNA  $\leq$ 100,000 copies/mL. This dose of Odefsey can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $<$ 50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.

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

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

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

<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.

# Tenofovir Disoproxil Fumarate (TDF, Viread)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Oral Powder:** 40 mg per 1 g of oral powder (one level scoop, measured with supplied dosing scoop equals 1 g oral powder)

**Tablets:** 150 mg, 200 mg, 250 mg, and 300 mg

### Fixed-Dose Combination Tablets

- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada tablet] Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada low-strength tablet]
  - Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg
  - Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg
  - Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg

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

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

## Dosing Recommendations

### Neonate and Infant Dose:

- Tenofovir disoproxil fumarate (TDF) has not been approved by the Food and Drug Administration or recommended for use in neonates and infants aged <2 years.

### Child (Aged ≥2 Years to <12 Years) Dose:<sup>a</sup>

- TDF 8 mg/kg per dose once daily

### 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)

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density<sup>a</sup>

## Special Instructions

- TDF oral powder formulation is available for patients who are unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: one level scoop = 1 g powder = TDF 40 mg.
- Mix TDF oral powder with 2 to 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



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 for Patients Aged ≥2 Years and Weighing ≥17 kg

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

### [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)-naïve 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 who have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.
- Administer with a meal of ≥500 calories.

### [Delstrigo] Doravirine/Emtricitabine/TDF

*Adult Dose:*

- One tablet once daily in ART-naïve adults. This dose of Delstrigo can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known

liquid. The powder may float on the top even after vigorous stirring.

- Although TDF can be administered without regard to food, food requirements vary depending on the other ARV drugs contained in an FDC tablet. Food requirements are listed with dosing recommendations and in the [Appendix A, Table 2](#) of the Drug Appendix.
- 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 15i. Antiretroviral Therapy—Associated Adverse Effects and Management Recommendations—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 in 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 TFV 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

mutations associated with resistance to the individual components of Delstrigo.

- Not studied in children or adolescents (see the [Doravirine](#) section for more information)

#### **[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-naïve 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 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.
- Symfi Lo has not been studied in children (SMR 1 to 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 to 3 who weigh ≥40 kg. Therapeutic drug monitoring is suggested by some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV when Symfi Lo is used in pediatric patients weighing ≥40 kg. See the [Efavirenz](#) section for more information.

#### **[Temixys] Lamivudine/TDF**

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

- One tablet once daily

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

*Child, Adolescent, and Adult Dose:*

information for directions on how to adjust the dose in accordance with CrCl.

- The FDCs Atripla, Complera, **Delstrigo**, **Symfi**, and Symfi Lo 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.

### Truvada Dosing Table

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

<sup>a</sup> See 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).

# Zidovudine (ZDV, Retrovir)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Syrup:** 10 mg/mL

**Capsule:** 100 mg

**Concentrate for Injection or Intravenous Infusion:** 10 mg/mL (Retrovir)

### Generic Formulations:

- 100 mg capsule
- 10 mg/mL syrup
- 300 mg tablet

### Fixed-Dose Combination Tablets:

- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

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

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

## Dosing Recommendations

**Note:** Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Table 12](#) for information about using ZDV to prevent perinatal transmission.

### Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth<sup>a</sup>

Gestational Age at Birth	Oral ZDV Dose								
≥35 weeks	<b>Birth to Age 4 Weeks</b> <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>								
	<b>Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth:</b>								
	<b>Note:</b> The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.								
	<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>	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
	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								
<b>Aged &gt;4 Weeks</b> <ul style="list-style-type: none"><li>• ZDV 12 mg/kg twice daily</li></ul>									

## Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia; macrocytosis with or without anemia.
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of ZDV) and myositis

## Special Instructions

- Give ZDV without regard to food.
- 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.
- 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

Gestational Age at Birth	Oral ZDV Dose
≥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 to 8 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;6 Weeks to 8 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 to 10 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;8 Weeks to 10 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 Zidovudine

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 mg to 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

#### [Combivir and Generic] Lamivudine/Zidovudine

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

- One tablet twice daily

#### [Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

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

- One tablet twice daily

function should be monitored for several months after patients with HBV infection stop taking 3TC.

#### Metabolism/Elimination

- ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.
- ZDV is phosphorylated intracellularly to active ZDV-triphosphate.

#### Zidovudine Dosing in Patients with Hepatic Impairment

- The dose of ZDV may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients who have impaired hepatic function.

#### Zidovudine Dosing in Patients with Renal Impairment

- A dose adjustment is required for ZDV in patients with renal insufficiency.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min and patients who are on hemodialysis.

<sup>a</sup> For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

## **Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)**

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant)

# Doravirine (DOR, Pifeltro)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Tablet:** 100 mg

### Fixed-Dose Combination Tablet:

- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

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

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

## Dosing Recommendations

### Child and Adolescent Dose:

- Doravirine (DOR) is not approved for use in children or adolescents aged <18 years.

### Adult (Aged ≥18 Years) Dose:

- DOR 100 mg 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 DOR.

### [Delstrigo] Doravirine (DOR)/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)

#### Adult (Aged ≥18 Years) Dose:

- One tablet once daily in 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 DOR.

## Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

## Special Instructions

- DOR can be taken with or without food.
- **Do not use** DOR with other non-nucleoside reverse transcriptase inhibitors.
- 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.
- 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 hepatitis B viral load should be monitored for several months after halting therapy with 3TC or TDF.

## Metabolism/Elimination

- DOR is metabolized by the enzyme cytochrome P450 3A.
- DOR has multiple interactions with several drugs (see Drug Interactions section below).

## Doravirine Dosing in Patients with Hepatic

**Impairment:**

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment.

**Doravirine Dosing in Patients with Renal Impairment:**

- 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.
- DOR administered with 3TC and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.



# Efavirenz (EFV, Sustiva)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Capsules:** 50 mg, 200 mg

**Tablet:** 600 mg

### Generic Formulations:

- 50 mg and 200 mg capsules
- 600 mg tablet

### Fixed-Dose Combination Tablets:

- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

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

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

## Dosing Recommendations

### Neonatal Dose:

- Efavirenz (EFV) is not approved for use in neonates.

### Pediatric Dose:

- EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

*Infants and Children Aged 3 Months to <3 Years and Weighing  $\geq 3.5$  kg:*

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of EFV in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.
- If the use of EFV is unavoidable due to a clinical situation, the Panel suggests using investigational doses of EFV in this age group (see Table A in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below).

## Selected Adverse Events

- Rash, which is generally mild and transient and appears to be more common in children than in adults
- 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
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation
- Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests.

## Special Instructions

- 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.
- 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.
- The Food and Drug Administration cautions that EFV should not be used during the first

*Children Aged ≥3 Years and Weighing ≥10 kg:*  
**Once-Daily Doses of Efavirenz by Weight**

<b>Weight</b>	<b>EFV Dose<sup>a,b</sup></b>
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] Efavirenz 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] 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.

**Note:** 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 ≥40 kg. The use of therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh ≥40 kg (see the Therapeutic Drug Monitoring section below).

trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the [Perinatal Guidelines](#) do not restrict use of EFV in female adolescents and adults who are pregnant or who may become pregnant.

**Instructions for Using the Efavirenz 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**

- CYP2B6 is the primary enzyme for EFV metabolism.
- CYP3A and CYP2B6 inducer *in vivo*
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450, particularly CYP2B6 polymorphisms. 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).

**Efavirenz 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.

# Etravirine (ETR, Intelence) (Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Tablets:** 25 mg, 100 mg, 200 mg

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

## Dosing Recommendations

### Neonate and Infant Dose:

- Etravirine (ETR) is not approved for use in neonates or infants.

### Child Dose:

- ETR is not approved for use in children aged <2 years.

### Etravirine Dosing Table for Antiretroviral Therapy-Experienced Children and Adolescents Aged 2 to 18 Years and Weighing $\geq 10$ kg

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
$\geq 30$ kg	200 mg

### Adult Dose for Antiretroviral Therapy-Experienced Patients:

- ETR 200 mg twice daily with food

## Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional symptoms, and sometimes, organ dysfunction, including hepatic failure

## Special Instructions

- ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
- 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.
- 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 than swallowing tablets whole. Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as developmentally able.

## Metabolism/Elimination

- 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.
- ETR is involved in multiple interactions with antiretroviral agents and other drugs (see Drug Interactions).

### Etravirine Dosing in Patients with Hepatic Impairment:

- 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.

**Etravirine Dosing in Patients with Renal Impairment:**

- No dose adjustment is required when using ETR in patients with renal impairment.

## Nevirapine (NVP, Viramune)

(Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Oral Suspension:** 10 mg/mL

**Tablets:** Immediate-release 200 mg tablets; extended-release (XR) 100 mg and 400 mg tablets

#### Generic Formulations:

- 10 mg/mL suspension
- Immediate-release 200 mg tablets
- XR 400 mg tablets

The oral suspension formulation of brand-name nevirapine (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.

### Dosing Recommendations

**Note:** Nevirapine (NVP) often is used to prevent perinatal transmission of HIV. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#).

#### Child and Adolescent Dose:

- In most situations, NVP is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.<sup>a</sup>

#### Immediate-Release Tablets and Oral Suspension

##### Gestational Age of 34 to 37 Weeks:

- NVP 4 mg/kg per dose twice daily for the first week, increasing to NVP 6 mg/kg per dose twice daily thereafter (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the Food and Drug Administration (FDA).

##### Gestational Age of ≥37 Weeks to Age of <1 Month:

- NVP 6 mg/kg per dose twice daily (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the FDA.
- See Special Considerations for Dosing: Neonates and Premature Infants below.

##### Aged ≥1 Month to <8 Years:

- NVP 200 mg per m<sup>2</sup> of body surface area 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).

### Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis<sup>b</sup>
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

### Special Instructions

- The oral suspension must be shaken well before administering and stored at room temperature.
- NVP can be given without regard to food.
- 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 (see [Major Toxicities below](#)).
- Extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >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).
- 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](#)).

### Aged ≥8 Years:

- NVP 120 mg to 150 mg per m<sup>2</sup> of body surface area 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 mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose can be left static to achieve the appropriate mg-per-m<sup>2</sup> dose as the child grows, if no adverse effects (AEs) 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 Nevirapine 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)

#### Adolescent and Adult Dose:

- NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.<sup>a,b</sup>

### Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed in patients who are also receiving NVP (see the [Lopinavir](#) section for more information).

## Metabolism/Elimination

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

### Nevirapine Dosing in Patients with Hepatic Impairment:

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

### Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

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

<sup>a</sup> NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP induces CYP 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 there are no rashes or other AEs 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 ≥1 month to <8 years is NVP 200 mg per m<sup>2</sup> of body surface area once daily for the first 14 days, followed by NVP 200 mg per m<sup>2</sup> of body surface area twice daily thereafter. However, in children aged ≤2 years, some experts initiate NVP without lead-in dosing (see [Dosing Considerations: Lead-In Dosing](#) and [Special Considerations for Dosing: Neonates and Premature Infants](#) 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—have occurred in patients who were taking NVP. These toxicities are less common in children than adults. The majority of 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.

# Rilpivirine (RPV, Edurant) (Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Tablets:** 25 mg

### Fixed-Dose Combination Tablets:

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg

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

### Co-Packaged Formulation:

- [Cabenuva] Cabotegravir 200 mg/ml and Rilpivirine 300 mg/mL suspension for intramuscular injection

When using the co-packaged formulation, refer to the [Cabotegravir](#) section for additional information.

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

## Dosing Recommendations

### Neonate and Infant Dose

- Rilpivirine (RPV) is not approved for use in neonates or infants.

### Children Aged <12 Years

- RPV is not approved for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

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

- RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to RPV and other antiretroviral (ARV) drugs in the new regimen.

### [Complera] Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (TDF)

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

- One tablet once daily with a meal in ART-naive 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 <50 copies/mL) for at least 6 months with no history of treatment failure and no known

## Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include drug reaction [or rash] with eosinophilia and systemic symptoms)
- Hepatotoxicity
- Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance

## Special Instructions

- **Do not start** RPV in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- **RPV concentrations are significantly increased when either RPV or dolutegravir (DTG)/RPV is administered with a moderate- or high-fat meal.** 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).
- **Do not use** RPV with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H2 receptor antagonists (e.g., cimetidine,

mutations associated with resistance to the individual components of Complera.

### [Juluca] Dolutegravir/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.
- Not approved for use in children or adolescents (see Simplification of Treatment section below).

### [Odefsey] Emtricitabine/Rilpivirine/Tenofovir Alafenamide (TAF)

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

- One tablet once daily with a meal in ART-naïve patients with HIV RNA ≤100,000 copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <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.

### [Cabenuva] Cabotegravir (CAB) and Rilpivirine (RPV)

#### Adult Dose

- Cabenuva is a two-drug co-packaged product for intramuscular injection (IM CAB and RPV) that is FDA approved as a complete regimen for the treatment of HIV-1 in adults with HIV RNA levels <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.
- Oral lead in dosing for at least 28 days is used to assess tolerability.
- Refer to [Cabotegravir](#) for dosing information.

famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.

- Use RPV with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see [CredibleMeds](#)).
- Screen patients for hepatitis B virus (HBV) infection before using fixed-dose combination (FDC) tablets that contain TDF or TAF. Severe acute exacerbation of HBV infection can occur when TDF or TAF are discontinued, see [Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide](#). Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with TDF or TAF is stopped in patients with HBV.
- Refer to [Cabotegravir](#) for special instructions when using cabotegravir (CAB) and RPV for intramuscular injection (IM CAB and RPV).

### Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate.
- Refer to [Cabotegravir](#) for information about the CAB and RPV regimen.

### Rilpivirine Dosing in Patients with Hepatic Impairment

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

### Rilpivirine Dosing in Patients with Renal Impairment

- RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.
- 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.
- The FDC tablet Complera **should not** be used in patients with creatinine clearance (CrCl) <50 mL/min, and the FDC tablet Odefsey **should not** be used in patients with CrCl <30



mL/min. Patients with CrCl <30 mL/min who are taking Juluca should be monitored closely.

- When using Complera, see the [TDF section](#) of the guidelines; when using Odefsey, see the [TAF section](#).

## **Protease Inhibitors (PIs)**

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)

# Atazanavir (ATV, Reyataz) (Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Powder Packet:** 50 mg/packet

**Capsules:** 150 mg, 200 mg, 300 mg

### Generic Formulations

- 150 mg, 200 mg, and 300 mg capsules

### Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg

**Capsules and powder packets are not interchangeable.**

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

## Dosing Recommendations

### Neonate Dose:

- Atazanavir (ATV) is not approved for use in neonates and infants aged <3 months. **ATV should not be administered** to neonates because of risks associated with hyperbilirubinemia (e.g., bilirubin-induced neurologic dysfunction).

### Infant and Child Dose

*Powder Formulation of Atazanavir:<sup>a</sup>*

- The powder formulation of ATV must be administered with ritonavir (RTV).
- The powder formulation is not approved for use in infants aged <3 months or weighing <5 kg.

### Atazanavir Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥5 kg<sup>a</sup>

Weight	Once-Daily Dose
5 kg to <15 kg	ATV 200 mg (four packets) plus RTV 80 mg (1 mL oral solution), with food
15 kg to <25 kg <sup>b</sup>	ATV 250 mg (five packets) plus RTV 80 mg (1 mL oral solution), both with food

*Capsule Formulation of Atazanavir:<sup>a</sup>*

- ATV capsules are not approved for use in children aged <6 years or weighing <15 kg.

### Atazanavir Capsule Dosing Table for Children and Adolescents Aged ≥6 Years and Weighing ≥15 kg

Weight	Once-Daily Dose
5 kg to <15 kg	ATV 200 mg (four packets) plus RTV 80 mg (1 mL oral solution), with food
15 kg to <25 kg <sup>b</sup>	ATV 250 mg (five packets) plus RTV 80 mg (1 mL oral solution), both with food

## Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (occurs primarily with RTV boosting)

## Special Instructions

- Administer ATV with food to enhance absorption.
- Capsules and powder packets **are not interchangeable**.
- Do not open capsules.
- 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).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the [ATV package insert](#)).
- 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)-naive 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.

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

### ART-Naive Patients Who Are Unable to Tolerate Ritonavir

*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, since it must be administered with RTV.
- For the capsule formulation, while the Food and Drug Administration (FDA) does not recommend the use of unboosted ATV in children aged <13 years, adolescents aged ≥13 years and weighing ≥40 kg may be prescribed unboosted ATV if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).
- To achieve target drug concentrations, adolescents may require doses of ATV that are higher than those recommended for use in adults (see Pediatric Use below).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of unboosted ATV.

### ART-Naive and ART-Experienced Patients

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

- Atazanavir/ritonavir (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] Atazanavir/Cobicistat

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

- One tablet once daily with food

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 virus or hepatitis C virus infections and patients who had marked elevations in transaminase levels before treatment may have an increased risk of further elevations in transaminase levels or hepatic decompensation.
- ATV oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.

### Powder Administration

- Mix ATV oral powder with at least one 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 glucuronyl transferase 1A1.

### Atazanavir 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.

### Atazanavir Dosing in Patients with Renal Impairment

- No dose adjustment is required for patients with renal impairment.
- ATV should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

## Darunavir (DRV, Prezista) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Oral Suspension:** 100 mg/mL

**Tablets:** 75 mg, 150 mg, 600 mg, 800 mg

#### Fixed-Dose Combination Tablets:

- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg

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

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

### Dosing Recommendations

**Note:** Darunavir (DRV) should not be used without a pharmacokinetic (PK) 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  $\geq 40$  kg and in adults.

#### Neonate/Infant Dose:

- DRV is not approved for use in neonates/infants.

#### Child Dose

*Aged <3 Years:*

- **Do not use DRV in children aged <3 years or weighing  $\leq 10$  kg.** In juvenile rats, DRV caused convulsions and death; and these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

*Aged  $\geq 3$  Years to <12 Years:*

- Dosing recommendations in the table below are for children aged  $\geq 3$  years to <12 years and weighing  $\geq 10$  kg who are antiretroviral therapy (ART)-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.

### Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headache
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

### Special Instructions

- Once-daily DRV is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data, and limited clinical experience exist with this dosing schedule in this age group.
- Once-daily DRV **should not be used** if any one of the following resistance-associated mutations is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.
- DRV must be administered with food, which increases DRV plasma concentrations by 30%.
- DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.
- 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

**Twice Daily Darunavir and Ritonavir Doses for Children Aged 3 Years to <12 Years and Weighing ≥10 kg**

Weight	Dose (Twice Daily with Food) <sup>a</sup>
10 kg to <11 kg <sup>b</sup>	DRV 200 mg (2.0 mL) plus RTV 32 mg (0.4 mL)
11 kg to <12 kg <sup>b</sup>	DRV 220 mg (2.2 mL) plus RTV 32 mg (0.4 mL) <sup>c</sup>
12 kg to <13 kg <sup>b</sup>	DRV 240 mg (2.4 mL) plus RTV 40 mg (0.5 mL) <sup>c</sup>
13 kg to <14 kg <sup>b</sup>	DRV 260 mg (2.6 mL) plus RTV 40 mg (0.5 mL) <sup>c</sup>
14 kg to <15 kg	DRV 280 mg (2.8 mL) plus RTV 48 mg (0.6 mL) <sup>c</sup>
15 kg to <30 kg	DRV 375 mg (combination of tablets or 3.8 mL) <sup>d</sup> plus RTV 48 mg (0.6 mL) <sup>d</sup>
30 kg to <40 kg	DRV 450 mg (combination of tablets or 4.6 mL) <sup>d,e</sup> plus RTV (100 mg tablet or powder or 1.25 mL) <sup>b</sup>
≥40 kg	DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or 1.25 mL)

**Child and Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With Darunavir Resistance**

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

**Child and Adolescent (Aged ≥12 years and Weighing ≥40 kg)<sup>e</sup> and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated With Darunavir Resistance**

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

**Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance**

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

**Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir 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.

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 fixed-dose combination (FDC) tablets that contain emtricitabine (FTC) or tenofovir alafenamide (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.

**Darunavir 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.

**Darunavir Dosing in Patients with Renal Impairment**

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

**[Prezcobix] Darunavir/Cobicistat**

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

- One tablet once daily with food

**[Symtuza] Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)**

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

- One tablet once daily with food in ARV-naive 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 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> Note that the dose in children weighing 10 kg to 15 kg is DRV 20 mg/kg plus RTV 3 mg/kg of body weight per dose, which is higher than the weight-adjusted dose in children with higher weights.
- <sup>c</sup> RTV 80 g/mL oral solution.
- <sup>d</sup> The volumes for the 375-mg and 450-mg DRV doses are rounded for suspension-dose convenience.
- <sup>e</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  $\geq 30$  kg to  $< 40$  kg (see Table B below).
- <sup>f</sup> See the [Cobicistat](#) section for important information about toxicity, drug interactions, and monitoring in patients who receive COBI.

## Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

#### Oral Solution:

- [Kaletra] Lopinavir 80 mg/mL and ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

#### Film-Coated Tablets:

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

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

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

### Dosing Recommendations

#### Neonate (Aged <14 Days) Dose:

- Lopinavir/ritonavir (LPV/r) is not approved by the 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. However, when **preferred nevirapine and raltegravir-based regimens are not an option** for neonates who have not met these age thresholds, some members of The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) would consider using LPV/r with careful **clinical and laboratory monitoring** (see [Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children](#)). This use of LPV/r is based on limited research and clinical experience. The potential benefit of using LPV/r in premature infants must be carefully balanced with the risk of metabolic and cardiac toxicity (**See Pediatric Use and Major Toxicities below**).

#### Dosing for Individuals Who Are Not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

##### Infant (Aged 14 Days–12 Months) Dose:

- Once-daily dosing **is not recommended**.
- 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 <12 months is associated with lower LPV

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, alteration of taste
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and Torsades de Pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).

### Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets.**
- LPV/r oral solution should be administered with food, because a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Formulations).
- 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



trough levels than those found in adults; LPV dosing should be adjusted for growth at frequent intervals (see text below). Also see text for information on transitioning infants to the lower mg per m<sup>2</sup> dose.

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- Once-daily dosing **is not recommended**.
- 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 <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥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 text 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 ≥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 Lopinavir 100 mg/Ritonavir 25 mg Pediatric Tablets in Children and Adolescents**

	Recommended Number of LPV/r 100 mg/25 mg Tablets Given Twice Daily	
<b>Dosing Target</b>	300 mg/m <sup>2</sup> per dose given twice daily	230 mg/m <sup>2</sup> per dose given twice daily
<b>Body Weight</b>		
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.

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.

**Lopinavir/Ritonavir Dosing in Patients with Hepatic Impairment:**

- LPV/r is primarily metabolized by the liver. 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. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

<sup>b</sup> In patients who weigh >45 kg and who are receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (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 >18 Years) Dose:*

- LPV/r 800 mg/200 mg once daily; *or*
- LPV/r 400 mg/100 mg twice daily
- **Do not use** once-daily dosing in children; adolescents; in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV; or in patients with three or more LPV-associated mutations (see Special Instructions for a list of mutations).

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

- LPV/r 400 mg/100 mg twice daily

**Dosing for Individuals Receiving Concomitant Nevirapine or Efavirenz:**

- 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 18 Years) Dose:*

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

*Adult (Aged >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**.

**Lopinavir/Ritonavir Used in Combination with Maraviroc**

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

## Entry and Fusion Inhibitors

Fostemsavir (FTR, Rukobia)

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

# Fostemsavir (FTR, Rukobia) (Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Extended-release tablet: 600 mg**

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

### Dosing Recommendations

#### Child and Adolescent Dose

- The safety and efficacy of using fostemsavir (FTR) in children and adolescents aged <18 years have not been established.

#### Adult Dose

- One tablet twice daily

### Selected Adverse Events

- QTc prolongation with higher than recommended dosages<sup>1</sup>
- Increased hepatic transaminases in patients with Hepatitis B or Hepatitis C co-infection

### Special Instructions

- Can be taken with or without food.
- Extended-release tablet must be swallowed whole. Do not chew, crush, or split tablets.
- Should not be co-administered with strong cytochrome P450 (CYP) 3A4 inducers of metabolism, such as rifampin, carbamazepine, phenytoin, and phenobarbital
- Potential for multiple drug interactions. Check concomitant medications before prescribing FTR.
- Tablets have slight odor similar to vinegar.

### Metabolism/Elimination

- FTR tromethamine is a prodrug of temsavir (TMR), an HIV-1 gp120-directed attachment inhibitor.
- 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 UGT (<1% of oral dose).
- TMR is a substrate of CYP3A, esterases, P-glycoprotein, and breast cancer resistance protein (BCRP).
- TMR is an inhibitor of organic anion transporter (OAT) P1B1 and OATP1B3; TMR and two of its metabolites are inhibitors of BCRP.

### Fostemsavir Dosing in Patients with Hepatic Impairment

- No dose adjustment is required in patients with mild to severe hepatic impairment.

### Fostemsavir Dosing in Patients with Renal Impairment

- No dose adjustment is required in patients with renal impairment or those on hemodialysis.

## Ibalizumab (IBA, Trogarzo)

(Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Single-Dose Vial for Intravenous Administration:** 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.

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

### Dosing Recommendations

#### Child and Adolescent Dose:

- The safety and efficacy of using ibalizumab (IBA) in children and adolescents has not been established.

#### Adult Dose:

- A single loading dose infusion of IBA 2,000 mg administered intravenously (IV) over 30 minutes is followed by a maintenance dose of IBA 800 mg administered IV over 15 minutes every 2 weeks.
- 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.
- IBA is used in combination with other antiretroviral drugs.

### Selected Adverse Events

- Diarrhea, dizziness, nausea, rash
- Immune reconstitution inflammatory syndrome
- Potential for immunogenicity in the form of anti-IBA antibodies

### Special Instructions

- The solution in the vial must be diluted in 0.9% sodium Chloride Injection by IV infusion.
- 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.
- 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.
- Diluted solution is administered as an IV infusion, not as a bolus or IV push.

### Metabolism/Elimination

- Monoclonal antibodies are metabolized to peptides and amino acids.

# Maraviroc (MVC, Selzentry)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Oral Solution:** 20 mg/mL

**Tablets:** 25 mg, 75 mg, 150 mg, 300 mg

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

## Dosing Recommendations

### Neonate and Infant Dose:

- Maraviroc (MVC) is approved by the Food and Drug Administration (FDA) for use, in combination with other antiretroviral agents, for the treatment of CCR5-tropic HIV-1 infection in infants born full term weighing  $\geq 2$  kg, children, adolescents, and adults.

### Recommended Maraviroc Dose for Full-Term Infants and Treatment-Experienced Children and Adolescents Weighing $\geq 2$ kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when MVC is given with non-interacting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (ENF), and raltegravir (RAL)			
2 kg to <4 kg	30 mg	1.5 mL	NA
4 kg to <6 kg	40 mg	2 mL	NA
6 kg to <10 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
10 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
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)			
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	75–80 mg	4 mL	One 75-mg tablet

## Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

## Special Instructions

- MVC is recommended for use in patients who only have CCR5-tropic HIV-1. Before using MVC, conduct testing with an HIV tropism assay (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)) 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.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

## Metabolism/Elimination

- MVC is a substrate of CYP3A4. If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of MVC should be adjusted accordingly.

## Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering MVC to patients with hepatic impairment; MVC concentrations may be increased in these

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.		

### Recommended Maraviroc Dose for Adults: Tablets

When Coadministered With:	Dose
Non-interacting 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

patients.

### Maraviroc Dosing in Patients with Renal Impairment:

- There are no data to recommend specific doses of MVC for pediatric patients with mild or moderate renal impairment. MVC is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease who are on regular hemodialysis and who are receiving potent CYP3A inhibitors.
- Refer to the manufacturer's prescribing information for the appropriate doses to use in adult patients with renal impairment.

## **Integrase Inhibitors**

Bictegravir (BIC)

**Cabotegravir (CAB, Vocabria)**

Dolutegravir (DTG, Tivicay)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)



## Bictegravir (BIC) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

Bictegravir is only available in a fixed-dose combination (FDC) tablet.

#### Fixed-Dose Combination Tablet:

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg

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

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

### Dosing Recommendations

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

##### Neonate or Child Aged <2 years and Weighing <14 kg:

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

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

- Currently, data are limited on the appropriate dose of Biktarvy in children aged <6 years and weighing 14 to <25 kg. Studies are being conducted to identify the safety and efficacy of a low-dose Biktarvy tablet. See the Pediatric Use section below.

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

- One tablet once daily with or without food. The Food and Drug Administration approved Biktarvy for use only in antiretroviral therapy-naïve patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen 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 (the Panel) with HIV members recommend the use of Biktarvy in patients with prior treatment failure and who have the virus containing the M184V mutation (see Efficacy in Clinical Trials in Adults below).

### Selected Adverse Events

- Diarrhea, nausea, headache

### Special Instructions

- Administer Biktarvy with or without food. See Drug Interactions below for guidance when administering Biktarvy with antacids or iron or calcium supplements.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (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.

### Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.

### Biktarvy Dosing in Patients with Hepatic Impairment

- Biktarvy **is not recommended** for use in patients with severe hepatic impairment.

### Biktarvy Dosing in Patients with Renal Impairment

- Biktarvy **is not recommended** for use in patients with estimated creatinine clearance <30 mL/min.

## Cabotegravir (CAB, Vocabria)

### Cabotegravir and Rilpivirine for Intramuscular Injections (IM CAB and RPV, Cabenuva) (Last updated April 7, 2021; last reviewed April 7, 2021)

#### Formulations

Tablets:

Cabotegravir: 30 mg

#### Co-Packaged Formulation

- [Cabenuva] Cabotegravir 200 mg/mL and rilpivirine 300 mg/mL suspension for intramuscular injection

When using the co-packaged formulation, refer to the [Rilpivirine](#) section for additional information.

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

#### Dosing Recommendations

##### Pediatric Dose

- Cabotegravir (CAB) tablets and co-packaged cabotegravir and rilpivirine intramuscular injections (IM CAB and RPV) are not approved by the Food and Drug Administration (FDA) for use in children or adolescents aged <18 years.

##### [Cabenuva] Cabotegravir and Rilpivirine (IM CAB and RPV)

###### Adult Dose

- CAB and RPV is a two-drug co-packaged product for intramuscular injection that is FDA approved as a complete regimen for the treatment of HIV-1 in adults with HIV RNA levels <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.
- Oral (PO) lead-in dosing with CAB and RPV for at least 28 days is used to assess tolerability.

###### Oral Lead-In Dosing

- CAB 30 mg PO and RPV 25 mg PO once daily with a meal for at least 28 days.

###### Loading Dose to Be Given on Last Day of Oral therapy

- CAB 600 mg (3 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites.

###### Continuation Therapy to Begin 1 Month After the Loading Dose

- CAB 400 mg (2 mL) and RPV 600 mg (2 mL), given as two separate injections in separate ventrogluteal sites once a month with allowance for a  $\pm 7$ -day

#### Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include drug reaction with eosinophilia and systemic symptoms) or hypersensitivity
- Hepatotoxicity
- Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance
- Injection site reactions
- Creatine phosphokinase elevation following intramuscular injection
- Weight gain

#### Special Instructions

- 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.
- 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.

administration window.

Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1½ inch intramuscular 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 BMIs over 30 kg/m<sup>2</sup>.

- IM CAB and RPV is a complete regimen. Coadministration with other ARV drugs is not recommended.
- When 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 IM CAB and RPV.
- Use CAB and RPV with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see [CredibleMeds](#)).

### **Metabolism/Elimination**

- CAB is metabolized by uridine diphosphate-glucuronosyl transferase (UGT)1A1.
- RPV is a cytochrome P450 3A substrate.

### **Dosing in Patients with Hepatic Impairment**

- No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate hepatic impairment.

### **Dosing in Patients with Renal Impairment**

- RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.
- No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate renal impairment. However, IM 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.

# Dolutegravir (DTG, Tivicay, Tivicay PD)(Last updated February 12, 2021; last reviewed February 12, 2021)

## Formulations

### Tablets:

Dispersible tablets for oral suspension [Tivicay PD] 5 mg

Film-coated tablets [Tivicay] 10 mg, 25 mg, 50 mg

### Fixed-Dose Combination Tablets:

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

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

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

## Dosing Recommendations

### Neonate Dose:

- Dolutegravir (DTG) is not approved by the Food and Drug Administration (FDA) for use in neonates.

### Pediatric and Adult Dose:

#### [Tivicay PD] Dolutegravir dispersible tablets

- **Infant (Aged  $\geq 4$  weeks and Weighing  $\geq 3$  kg) and Child and Adolescent Dose:** DTG dispersible tablets are approved by the FDA for use in pediatric patients who are treatment-naïve or treatment-experienced but naïve to integrase strand transfer inhibitor (INSTI) treatment:

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
$\geq 20$ kg	30 mg once daily	6

<sup>a</sup> If certain uridine diphosphate glucuronyl transferase (UGT) 1A or cytochrome P450 (CYP) 3A inducers are coadministered, administer DTG dispersible tablets twice daily.

#### [Tivicay] Dolutegravir film-coated tablets

**Child and Adolescent (Weighing  $\geq 14$  kg) and Adult Dose:**

## Selected Adverse Events

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness
- Rare cases of hypersensitivity reactions, including rash and drug reaction (or rash) with eosinophilia and systemic symptoms, constitutional symptoms, and organ dysfunction (including liver injury).

## Special Instructions

- DTG may be taken without meals.
- 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.
- 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

- For use in patients who are treatment-naive or treatment-experienced but naive to INSTI treatment.
- Do not use DTG film-coated tablets in patients weighing <14 kg.
- **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  $\geq 14$  kg who can swallow tablets:

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

<sup>a</sup> If certain UGT1A or CYP3A inducers are coadministered, administer DTG tablets twice daily.

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.

### [Dovato] Dolutegravir/Lamivudine

*Adult Dose:*

- One tablet once daily with or without food as a complete regimen in antiretroviral (ARV)-naive adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete 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 (see the Simplification of Treatment section below).

### [Juluca] Dolutegravir/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

- 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).
- No data exist regarding dispersion in breast milk or any other vehicle.
- In patients who have difficulty swallowing 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 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain lamivudine (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.

## Metabolism/Elimination

- UGT1A1 and CYP3A substrate. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes may increase DTG plasma concentrations.

### Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of a 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**

### Dolutegravir 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

associated with resistance to the individual components of Juluca.

- Juluca is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen (see the Simplification of Treatment section below).

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

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

- One tablet once daily with or without food.
- 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.
- See the [Abacavir section](#) for special instructions about testing for abacavir (ABC) hypersensitivity.
- The FDA-approved dose for pediatric patients weighing  $\geq 40$  kg is one tablet once daily, **but the Panel recommends this FDC can be used for patients  $\geq 25$  kg.**

- with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance  $< 30$  mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.
- **FDC tablets containing 3TC or ABC should not be used in patients who have creatinine clearance  $< 50$  mL/min or who are on dialysis.**

## Elvitegravir (EVG) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Tablet:** Discontinued by the manufacturer. Elvitegravir is available only in fixed-dose combination (FDC) tablets.

#### Fixed-Dose Combination Tablets:

- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

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

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

### Dosing Recommendations

#### [Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

*Child (Weighing <14 kg) Dose:*

- No data exist on the dosing of EVG/c/F/TAF for children weighing <14 kg.

*Child (Weighing ≥14 to <25 kg)*

- Data are currently limited on the dosing of a pediatric EVG/c/FTC/TAF formulation in children ≥14 kg to <25 kg. Studies are currently being conducted to assess the safety and efficacy of a fixed low-dose combination tablet.

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

- One tablet once daily with food in antiretroviral therapy (ART)-naive patients. This dose of Genvoya also can be used to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 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.

#### [Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

*Child and Adolescent (Weighing <35 kg) Dose:*

- There are no data on the appropriate dose of Stribild for children or adolescents weighing <35 kg.

### Selected Adverse Events

#### Genvoya- and Stribild-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

*Elvitegravir-Associated Adverse Events:*

- Diarrhea

*TAF-Specific Adverse Events:*

- Increased levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol

*TDF-Specific Adverse Events:*

- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density
- Flatulence

*Cobicistat-Specific Adverse Events:*

- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine

### Special Instructions

- Administer both Genvoya and Stribild with food.
- 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.
- When using Stribild, which contains TDF,

*Adolescent (Weighing  $\geq 35$  kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose:*

- One tablet once daily with food in ART-naive patients. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable 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.

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  $> 0.4$  mg/dL should be closely monitored for renal safety.

- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC), TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF.
- For information on crushing and cutting tablets, please see [this table](#) from Toronto General Hospital.

### **Metabolism/Elimination**

- EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- EVG **is available only in combination** with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the [TDF](#) and [TAF](#) sections for further details on these components.

### **Elvitegravir Dosing in Patients with Hepatic Impairment:**

- Stribild and Genvoya **should not be used** in patients with severe hepatic impairment.

### **Elvitegravir Dosing in Patients with Renal Impairment:**

- Stribild **should not be initiated** in patients with estimated CrCl  $< 70$  mL/min, and it should be discontinued in patients with estimated CrCl  $< 50$  mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya **should not be initiated** in patients with estimated CrCl  $< 30$  mL/min.



# Raltegravir (RAL, Isentress)

(Last updated April 7, 2021; last reviewed April 7, 2021)

## Formulations

**Tablet:** 400 mg (film-coated poloxamer tablet)

**High-Dose (HD) Tablet:** 600 mg (film-coated poloxamer tablet)

**Chewable Tablets:** 100 mg (scored) and 25 mg

**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.

**Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.**

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

## Dosing Recommendations

**Note:** No dosing information is available for preterm infants or infants weighing <2 kg at birth. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and Table 12 for information about using raltegravir (RAL) for the prevention of perinatal HIV transmission.

### Neonate (Weighing ≥2 kg) Dose<sup>a</sup>

#### Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks

Neonates Aged ≥37 Weeks and Weighing ≥2 kg:

Weight	Volume (Dose) of Suspension
<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

**Note:** <sup>a</sup>RAL is metabolized by uridine diphosphate glucuronyl transferase (UGT1A1), and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4–6 weeks of life.

If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose should be delayed until 24–48 hours after birth.

### Infant >4 weeks of age and Child (Weighing ≥3 kg to <20 kg) Dose:

- For children weighing 3–20 kg, either oral suspension or chewable tablets can be used.

## Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

## Special Instructions

- RAL can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any RAL formulations.
- Significant drug interactions are more likely to occur when the RAL HD formulation is used once daily. **The following drugs should not be coadministered with once daily RAL HD dosing:** calcium carbonate, rifampin, tipranavir/ritonavir, and etravirine.
- Chewable tablets can be chewed, crushed (before administration), or swallowed whole.
- Film-coated tablets, including HD tablets, must be swallowed whole.
- 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

## Raltegravir Oral Suspension Dosing Table for Patients Aged >4 Weeks<sup>a</sup>

**Note:** The maximum dose of oral suspension is 10

Weight	Twice-Daily Volume (Dose) of Suspension
3 kg to <4 kg	2.5 mL (25 mg) <b>twice daily</b>
4 kg to <6 kg	3 mL (30 mg) <b>twice daily</b>
6 kg to <8 kg	4 mL (40 mg) <b>twice daily</b>
8 kg to <10 kg	6 mL (60 mg) <b>twice daily</b>
10 kg to <14 kg	8 mL (80 mg) <b>twice daily</b>
14 kg to <20 kg	10 mL (100 mg) <b>twice daily</b>

<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.

mL (RAL 100 mg) twice daily.

### Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and High-Dose 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.

*Children and Adolescents Weighing ≥40 kg:*

- Two RAL 600-mg HD tablets (1,200 mg) once daily
- This dose is for antiretroviral therapy-naïve or virologically suppressed patients who are on an initial dose of RAL 400 mg twice daily.

### Chewable Tablet Dosing Table<sup>a</sup>

**Note:** The maximum dose of chewable tablets is RAL 300 mg twice daily.

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	1 ½ tablets <sup>b</sup> (100 mg)
28 kg to <40 kg	RAL 200 mg	2 tablets (100 mg)

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 (for example, 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 mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. 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, as the volume for the required dose is much smaller than 10 mL.

### Metabolism/Elimination

- UGT1A1-mediated glucuronidation

### Raltegravir 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.
- No studies have been conducted on the use of RAL HD in patients with hepatic impairment. Therefore, administering RAL HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on RAL pharmacokinetics has not been studied.

≥40 kg	RAL 300 mg	3 tablets (100 mg)
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<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.

<sup>b</sup> The RAL 100-mg chewable tablet can be divided into equal halves.

**Raltegravir Dosing in Patients with Renal Impairment:**

- No dose adjustment is necessary in patients with any degree of renal impairment.

## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

## Cobicistat (COBI, Tybost)

(Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

Tablet: 150 mg

#### Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg

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

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

### Dosing Recommendations

#### Cobicistat is a Pharmacokinetic Enhancer:

- The only use of cobicistat (COBI) is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase strand transfer inhibitors. COBI **is not interchangeable** with ritonavir (RTV).

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

- COBI 150 mg with atazanavir (ATV) 300 mg administered at the same time and with food

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

- COBI 150 mg with darunavir (DRV) 800 mg administered at the same time and with food

#### [Evotaz] Atazanavir/Cobicistat

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

- One tablet once daily with food
- Use in combination with other Antiretroviral (ARV) drugs.

#### [Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

*Child (Weighing  $\geq 14$  to  $< 25$  kg):*

- Limited data currently exist on the appropriate dose of Genvoya in children  $\geq 14$  kg to  $< 25$  kg. Studies are currently being conducted to assess the safety and efficacy of a low-dose tablet with elvitegravir (EVG) 90 mg/COBI 90

### Selected Adverse Events

- COBI is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function.

### Special Instructions

- COBI 150 mg **is not interchangeable** with RTV, but it has a PK boosting effect that is comparable to RTV 100 mg.
- 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.
- **Do not administer** COBI with RTV or with FDC tablets that contain COBI.
- COBI **is not recommended** for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Using COBI with PIs other than once-daily ATV 300 mg or DRV 800 mg **is not recommended**.
- Patients with a confirmed increase in serum creatinine  $> 0.4$  mg/dL from baseline should be closely monitored for renal safety.
- 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 [Table 15i—Nephrotoxic Effects](#)). In patients who are at risk of renal impairment, serum phosphate should also be monitored.

mg/emtricitabine (FTC) 120 mg/TAF 6 mg.

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

- One tablet once daily with food

#### **[Prezcobix] Darunavir/Cobicistat**

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

- One tablet once daily with food
- Use in combination with other ARV drugs.

#### **[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)**

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

- One tablet once daily with food
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

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

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

- One tablet once daily with food

- For information on crushing and cutting tablets, please see [this table](#) from Toronto General Hospital.

### **Metabolism/Elimination**

- COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

### **Cobicistat Dosing in Patients with Hepatic Impairment:**

- 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.<sup>1</sup>
- Genvoya, Prezcobix, Stribild, and Symtuza **are not recommended** in patients with severe hepatic impairment.<sup>1</sup>
- Evotaz **is not recommended** in patients with any degree of hepatic impairment.

### **Cobicistat Dosing in Patients with Renal Impairment:**

- 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.<sup>1</sup>
- The use of COBI plus TDF **is not recommended** in patients with creatinine clearance (CrCl)  $< 70$  mL/min. Dose adjustments for TDF are required for patients with CrCl  $< 50$  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.<sup>1</sup>
- 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. The dose adjustments required for emtricitabine and TDF in these patients cannot be achieved with an FDC tablet.
- Neither Genvoya nor Symtuza should be initiated in patients with estimated CrCl  $< 30$  mL/min.

## Ritonavir (RTV, Norvir) (Last updated April 7, 2021; last reviewed April 7, 2021)

### Formulations

**Oral Powder:** 100 mg per packet

**Oral Solution:** 80 mg/mL. Oral solution contains 43% (v/v) ethanol and approximately 27% (w/v) propylene glycol.

**Tablets:** 100 mg

#### Generic Formulation

- 100 mg tablets

#### Fixed-Dose Combination Solution:

- [Kaletra] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.

#### Fixed-Dose Combination Tablets:

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

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

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

### Dosing Recommendations

#### Ritonavir as a Pharmacokinetic Enhancer:

- Ritonavir (RTV) is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of RTV varies and is specific to the drug combination selected. See other sections of the [Drug Appendix](#) 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 pharmacokinetic enhancer of other PIs.

#### Formulation Considerations:

- The RTV oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least RTV 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- RTV oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Hyperglycemia
- Fat maldistribution

### Special Instructions

- Administer RTV with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** RTV with cobicistat (COBI) or drugs that contain COBI (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).
- **Do not refrigerate** RTV oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- RTV oral powder should be mixed with a soft food (e.g., apple sauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste.

### **[Kaletra] Lopinavir/Ritonavir**

*Infant, Child, Adolescent, and Adult Dose:*

- See the [Lopinavir/Ritonavir](#) section of the [Drug Appendix](#).

Administer or discard the mixture within 2 hours of mixing.

#### **To Increase Tolerability of Ritonavir Oral Solution or Oral Powder in Children:**

- Mix the solution or powder with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering RTV, give a child ice chips, a Popsicle, 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>
- After administration, give foods with strong tastes (e.g., maple syrup, cheese).
- Check a child's food allergy history before making these recommendations.
- Counsel caregivers or patients that the bad taste will not be completely masked.

#### **Metabolism/Elimination**

- Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein.

#### **Ritonavir Dosing in Patients with Hepatic Impairment:**

- RTV is primarily metabolized by the liver.
- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- There are no data 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.



## Archived Drugs

### *Overview*

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

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

## Didanosine (ddl, Videx) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Pediatric Oral Solution:** 10 mg/mL

**Enteric-Coated (EC) Delayed-Release Capsules (EC Beadlets):** 125 mg, 200 mg, 250 mg, and 400 mg

### Generic Formulations

**Delayed-Release Capsules:** 125 mg, 200 mg, 250 mg, and 400 mg

### Dosing Recommendations

**Note:** Didanosine **is no longer recommended** 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.

#### Neonate/Infant Dose (Aged 2 Weeks to <3 Months):

- 50 mg/m<sup>2</sup> of body surface area every 12 hours. See dosing section below for justification of this dose.

#### Infant Dose (Aged ≥3 Months to 8 Months):

- 100 mg/m<sup>2</sup> body surface area every 12 hours

#### Pediatric Dose of Oral Solution (Age >8 Months):

- 120 mg/m<sup>2</sup> body surface area every 12 hours
- Dose range: 90–150 mg/m<sup>2</sup> body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naïve children ages 3 years to 21 years, 240 mg/m<sup>2</sup> body surface area once daily (oral solution or capsules) has resulted in viral suppression.

#### Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥20 kg)

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

#### Adolescent and Adult Dose

Body Weight	Dose
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

### Selected Adverse Events

- Peripheral neuropathy
- Diarrhea, abdominal pain, nausea, and vomiting
- 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).
- Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir disoproxil fumarate or stavudine)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

### Special Instructions

- 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).
- 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.
- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.

### Metabolism/Elimination

- Renal excretion 50%

**Pediatric and Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate:**

- 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 [Adult and Adolescent Guidelines](#)).
- Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

## Enfuvirtide (T-20, Fuzeon) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

#### Lyophilized Powder for Injection:

- 108-mg vial of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

#### Convenience Kit:

- 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.

### Dosing Recommendations

#### Pediatric and Adolescent Dose (Aged 6–16 Years)

##### Children Aged <6 Years:

- Not approved for use in children aged <6 years

##### Children Aged ≥6 Years:

- 2 mg/kg (maximum dose 90 mg [1 mL]) twice daily injected subcutaneously (SQ) into the upper arm, anterior thigh, or abdomen

#### Adolescent (Aged >16 Years) and Adult Dose:

- 90 mg (1 mL) twice daily injected SQ into the upper arm, anterior thigh, or abdomen

### Selected Adverse Events

- Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in up to 98% of patients.
- Increased rate of bacterial pneumonia (unclear association).
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

### Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of SQ injections. Enfuvirtide injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject enfuvirtide immediately or keep refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours.
- Enfuvirtide must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions, apply ice or heat after injection or gently massage injection

site to better disperse the dose. There are reports of injection-associated neuralgia and paresthesia when alternative delivery systems, such as needle-free injection devices, are used.

- 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.

### **Metabolism/Elimination**

- Catabolism to constituent amino acids.

## Fosamprenavir (FPV, Lexiva) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Tablets:** 700 mg

**Oral Suspension:** 50 mg/mL

### Dosing Recommendations

#### Pediatric Dose (Aged >6 Months to 18 Years):

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants  $\geq 4$  weeks and for treatment-experienced infants  $\geq 6$  months; however, the Panel does not recommend use in infants aged  $< 6$  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.

**Note:** Once-daily dosing **is not recommended** for any pediatric patient.

#### Pediatric Dose (Aged $\geq 6$ Months to 18 Years):

#### Twice-Daily Dose Regimens by Weight for Pediatric Patients $\geq 6$ Months Using Fosamprenavir Oral Suspension with Ritonavir

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

<sup>a</sup> Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

### Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

### Special Instructions

- Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.
- Patients taking antacids should take fosamprenavir at least 1 hour before or after antacid use.
- 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.
- Shake oral suspension well before use. Refrigeration is not required.

### Metabolism/Elimination

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P (CYP) 450 3A4 inhibitor, inducer, and substrate.

**Note:** 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  $\geq 39$  kg. Ritonavir tablets can be used in patients weighing  $\geq 33$  kg.

**Adolescent and Adult Dose:**

- Dosing regimen depends on whether the patient is ARV-naïve or ARV-experienced.

*ARV-Naïve Patients*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily
- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily

*Protease-Inhibitor-Experienced Patients:*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily

**Note:** Once-daily administration of fosamprenavir plus ritonavir **is not recommended**.

Fosamprenavir Dosing in Patients with Hepatic Impairment:

- 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 package insert.

Fosamprenavir Dosing in Patients with Renal Impairment:

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

## Indinavir (IDV, Crixivan) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Capsules:** 100 mg, 200 mg, and 400 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Not approved for use in neonates/infants
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus)

#### Pediatric Dose:

- Not approved for use in children
- 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).

#### Adolescent and Adult Dose:

- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of indinavir in adolescents.

### Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

### Special Instructions

- When indinavir is given in combination with ritonavir, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate

#### Indinavir Dosing in Patients with Hepatic Impairment:

- 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.



## Nelfinavir (NFV, Viracept) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Tablets:** 250 mg and 625 mg

#### Dosing Recommendations

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **no longer recommends** nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

##### Neonate and Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

##### Pediatric Dose (Aged ≥2 Years):

- 45–55 mg/kg twice daily

##### Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily

#### Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Serum transaminase elevations

#### Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- 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.

#### Metabolism/Elimination

- Cytochrome P (CYP) 2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

## Saquinavir (SQV, Invirase) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Capsules:** 200 mg

**Tablets:** 500 mg

### Dosing Recommendations

#### Pediatric Dose:

- Not approved for use in infants, children, and adolescents aged <16 years.

#### Adolescent and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg twice daily

### Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)

### Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended; saquinavir is **contraindicated** in patients with a prolonged QT interval.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor
- 90% metabolized in the liver
- Use saquinavir with caution in patients who have hepatic impairment; no dose adjustment recommended.

## Stavudine (d4T, Zerit) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Powder for Oral Solution:** 1 mg/mL

**Capsules:** 15 mg, 20 mg, 30 mg, and 40 mg

#### Generic Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

### Dosing Recommendations

**Note:** 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).

#### Pediatric (Aged $\geq 14$ Days and Weighing $< 30$ kg) Dose:

- 1 mg/kg per dose twice daily

#### Adolescent (Weighing $\geq 30$ kg) and Adult Dose:

- 30 mg per dose twice daily

### Selected Adverse Events

- Associated with a higher risk of mitochondrial toxicity than other NRTI drugs
- 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.
- Facial/peripheral lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other NRTIs). The risk increases when stavudine is used in combination with didanosine.
- Dyslipidemia
- Insulin resistance, asymptomatic hyperglycemia
- Rapidly progressive ascending neuromuscular weakness (rare)

### Special Instructions

- Stavudine can be given without regard to food.
- Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.

### Metabolism/Elimination

- Renal excretion 50%. Decrease dose in renal dysfunction.
- Stavudine is phosphorylated intracellularly to the active metabolite stavudine triphosphate.

## Tipranavir (TPV, Aptivus) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Oral Solution:** 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL

**Capsules:** 250 mg

### Dosing Recommendations

**Note:** Tipranavir must be boosted with ritonavir. The ritonavir boosting dose used for tipranavir is higher than the doses used for other protease inhibitors.

#### Pediatric (Aged <2 Years) Dose:

- Not approved for use in children aged <2 years

#### Pediatric (Aged 2–18 Years) Dose:

**Note:** Not recommended for treatment-naive patients

#### Body Surface Area Dosing:

- 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)

#### Weight-Based Dosing:

- TPV/r 14 mg/kg/6 mg/kg, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)

#### Adult Dose:

- TPV/r 500 mg (as two 250-mg capsules)/200 mg, both twice daily
- **Note:** Not recommended for treatment-naive patients

### Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash (more common in children than adults)
- Nausea, vomiting, diarrhea
- Hepatotoxicity: elevated transaminases; clinical hepatitis
- Hyperlipidemia
- Hyperglycemia
- Elevated creatine phosphokinase

### Special Instructions

- Administer tipranavir and ritonavir together and with food.
- 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.
- Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- 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.
- 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.
- 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).

- Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.

### **Metabolism/Elimination**

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate
- P-glycoprotein substrate

#### Tipranavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required.

#### Tipranavir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required for mild hepatic impairment.
- Use of tipranavir is **contraindicated** in patients with moderate-to-severe hepatic impairment.