Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric Oral Solution: 20 mg/mL

Tablets: 300 mg (scored)

Fixed-Dose Combination Tablets:

- [*Epzicom*] Abacavir 600 mg plus lamivudine 300 mg
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [*Triumeq*] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Generic Formulations:

- Abacavir sulfate 300 mg tablets
- Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for infants aged <3 months.

Pediatric Dose:

Oral Solution (Aged ≥3 Months):

- 8 mg/kg (maximum 300 mg per dose) twice daily or 16 mg/kg once daily (maximum 600 mg per dose) (see text below)
- In infants and young children being treated with liquid formulations of abacavir, initiation with once daily abacavir is not generally recommended. In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) cell counts for more than 6 months (24 weeks) on abacavir twice daily, dose can be changed from twice daily to once daily (see text below).

Weight Band Dosing (Weighing ≥14 kg)

Scored 300-mg tablet.

Weight (kg)	Twice Daily AM Dose	Twice Daily PM Dose	Once Daily Dose
14 to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
≥20 to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1 ½ tablets (450 mg)
≥25 kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

Selected Adverse Events

- Hypersensitivity reactions can be fatal. Hypersensitivity reactions 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 and shortness of breath).
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of abacavir; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

- Test patients for the HLA-B*5701 allele before starting therapy to predict risk of HSR. Patients positive for the HLA-B*5701 allele should not be given abacavir. Patients with no prior HLA-B*5701 testing who are tolerating abacavir do not need to be tested.
- Warn patients and parents about risk of serious, potentially fatal hypersensitivity reactions. Occurrence of hypersensitivity reactions requires **immediate and permanent discontinuation** of abacavir. Do not re-challenge.
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.

- In patients who can be treated with pill formulations, therapy can be initiated with once daily administration. If therapy was initiated with twice daily liquid abacavir then it can be changed from twice daily to once daily in clinically stable patients with undetectable viral load and stable CD4 cell counts (without decline) for more than 6 months (24 weeks) (see text below).

Adolescent (Weighing ≥25 kg) and Adult Dose:

- 300 mg twice daily or 600 mg once daily.

[*Trizivir*] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weight ≥40 kg)/Adult Dose:

- One tablet twice daily.

[*Epzicom*] Abacavir plus Lamivudine

Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily.

[*Triumeq*] Abacavir plus Dolutegravir plus Lamivudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- One tablet once daily.

Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- Active metabolite is 82% renally excreted.
- Abacavir requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents), in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents) in patients with creatinine clearance (CrCl) <50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

Didanosine (ddI, Videx) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Formulations

Videx Pediatric Powder for Oral Solution: Reconstituted 10 mg/mL

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

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

Tablets for Oral Suspension: 100 mg, 150 mg, and 200 mg

Dosing Recommendations

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

- 50 mg/m^2 of body surface area every 12 hours
- Manufacturer recommends 100 mg/m^2 body surface area every 12 hours in this age range. The Panel members interpret pharmacokinetic (PK) data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 body surface area every 12 hours.

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

- 100 mg/m^2 body surface area every 12 hours

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

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

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

Body Weight (kg)	Dose (mg)
20 kg to <25 kg	200 mg once daily
25 kg to <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 TDF or stavudine)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of didanosine, administration of didanosine on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).
- Didanosine powder for oral solution and tablets for oral suspension contain antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of didanosine than for the enteric-coated formulation, which is protected from breakdown by gastric acid by the enteric

Adolescent and Adult Dose

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

Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate (TDF):

- This combination should be avoided if possible because of enhanced didanosine toxicity.
- No data on this combination in children or adolescents aged <18 years, but decrease in didanosine dose is recommended as in adults.

Adult Dose of Didanosine when Combined with TDF

Body Weight (kg)	Dose (mg)
<60 kg (limited data in adults)	200 mg once daily
≥60 kg	250 mg once daily

coating instead of co-formulation with antacids.

- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.
- If using tablets for oral suspension: Tablets are not to be swallowed whole. For full therapeutic effect, 2 tablets may be chewed or dispersed in water before administration. To disperse tablets: add 2 tablets to at least 1 ounce (30 mL) of water. Drink entire dispersion immediately. For children 1 or 2 tablets may be chewed or dispersed in water before administration.

Metabolism/Elimination

- Renal excretion 50%
- Dosing of didanosine in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

Emtricitabine (FTC, Emtriva) (Last updated April 26, 2016; last reviewed April 26, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric Oral Solution: 10 mg/mL

Capsules: 200 mg

Generic Formulations: None available

Fixed-Dose Combination Tablets:

- *[Truvada low strength tablet]*
  - Emtricitabine 100 mg plus tenofovir disoproxil fumarate (TDF) 150 mg
  - Emtricitabine 133 mg plus TDF 200 mg
  - Emtricitabine 167 mg plus TDF 250 mg
- *[Descovy]* Emtricitabine 200 mg plus tenofovir alafenamide (TAF) 25 mg
- *[Atripla]* Efavirenz 600 mg plus emtricitabine 200 mg plus TDF 300 mg
- *[Complera]* Emtricitabine 200 mg plus rilpivirine 25 mg plus TDF 300 mg
- *[Odefsey]* Emtricitabine 200 mg plus rilpivirine 25 mg plus TAF 25 mg
- *[Stribild]* Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg
- *[Genvoya]* Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg

Dosing Recommendations

Neonatal/Infant Dose (Aged 0 to <3 Months)

Oral Solution:

- 3 mg/kg once daily.

Pediatric Dose (Aged ≥3 Months to 17 Years)

Oral Solution:

- 6 mg/kg (maximum dose 240 mg) once daily; higher maximum dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.

Capsules (Weight >33 kg):

- 200 mg once daily.

Adolescent (Aged ≥18 Years) and Adult Dose

Oral Solution:

- 240 mg (24 mL) once daily.

Capsules:

- 200 mg once daily.

Combination Tablets

[Truvada tablet] Emtricitabine plus TDF

Truvada Tablets Dosing Table

Body Weight kg	FTC/TDF Tablet Once Daily
17 to <22	One 100 mg/150 mg tablet
22 to <28	One 133 mg/200 mg tablet
28 to <35	One 167 mg/250 mg tablet
Adolescent (Weighing ≥35 kg) and Adult Dose	One 200 mg/300 mg tablet

Selected Adverse Events

- Minimal toxicity
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus-coinfected patients who discontinue emtricitabine.
- Hyperpigmentation/skin discoloration on palms and/or soles

Special Instructions

- Although emtricitabine can be administered without regard to food, food requirements vary depending on the other antiretrovirals contained in a combination tablet. For Atripla (administer without food) and Complera (administer with a meal of at least 500 calories), refer to efavirenz or rilpivirine special instructions.
- Emtricitabine oral solution can be kept at room temperature up to 77˚ F (25˚ C) if used within 3 months; refrigerate for longer-term storage.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.
- Before using emtricitabine, screen patients for hepatitis B virus.

Metabolism/Elimination

- Limited metabolism: No cytochrome P (CYP) 450 interactions.

[Descovy] Emtricitabine plus TAF

Adolescent (Weighing >35 kg) and Adult Dose:

- 1 tablet once daily

[Atripla] Efavirenz plus Emtricitabine plus TDF 300 mg

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily.
- Administer without food
- See efavirenz section for pregnancy warning.

[Complera] Emtricitabine plus Rilpivirine plus TDF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily in treatment-naive patients with baseline plasma RNA <100,000 copies/mL or virologically suppressed patients with no history of virologic failure, resistance to rilpivirine and other antiretroviral (ARV) drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 500 calories.

[Odefsey] Emtricitabine plus Rilpivirine plus (TAF)

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no ARV treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

Adult Dose (Aged ≥18 Years):

- 1 tablet once daily in treatment-naive or virologically suppressed adults
- Administer with a meal.

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

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

- 1 tablet once daily with food in ARV treatment-naive patients or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

- Renal excretion 86%: Potential competition with other compounds that undergo renal elimination.
- Dosing of emtricitabine in patients with renal impairment: Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with creatinine clearance (CrCl) <50 mL/min or in patients requiring dialysis.
- Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring dialysis.
- Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.
- 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 in patients with estimated creatinine clearance (CrCl) below 30 mL per minute.

Lamivudine (3TC, Epivir) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric Oral Solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBV[a])

Tablets: 150 mg (scored) and 300 mg (generic); 100 mg (Epivir HBV[a])

Fixed-Dose Combination Tablets:

- [*Combivir and generic*] Lamivudine 150 mg plus zidovudine 300 mg
- [*Epzicom*] Abacavir 600 mg plus lamivudine 300 mg
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [*Triumeq*] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Generic Formulations

Tablets: 100 mg, 150 mg, and 300 mg

Dosing Recommendations

Neonate and Infant Dose (Aged <4 Weeks) for Treatment:

- 2 mg/kg twice daily

Note: Please see Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States for dosing used to prevent perinatal transmission.

Pediatric Dose (Aged ≥4 Weeks):

- 4 mg/kg (up to 150 mg) twice daily
- In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine is not generally recommended. Please refer to text for more detail.

Weight-Band Dosing (Weight ≥14 kg)
Scored 150 mg tablet

Weight	Twice Daily AM Dose	Twice Daily PM Dose	Once Daily Dose
14 to <20 kg	½ tablet (75 mg)	½ tablet (75 mg)	1 tablet 150 mg
≥20 to <25 kg	½ tablet (75 mg)	1 tablet (150 mg)	1 ½ tablets 225 mg
≥25 kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets 300 mg

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of lamivudine in the setting of chronic Hepatitis B virus infection.

Special Instructions

- Lamivudine can be given without regard to food.
- Store lamivudine oral solution at room temperature.
- Screen patients for Hepatitis B virus infection before administering lamivudine.

Metabolism/Elimination

- Renal excretion: Dosage adjustment required in renal insufficiency.
- Fixed-dose combination tablets should not be used in patients with creatinine clearance <50 mL/min, on dialysis, or with impaired hepatic function.

Adolescent and Adult Dose:
Body Weight <25 kg:

- 4 mg/kg (up to 150 mg) twice daily

Body Weight ≥25 kg:

- 150 mg twice daily or 300 mg once daily

[*Combivir and Generic*] Lamivudine plus Zidovudine
Adolescent (Weighing ≥30 kg) and Adult Dose:

- 1 tablet twice daily

[*Trizivir and Generic*] Abacavir plus Lamivudine plus Zidovudine
Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet twice daily.

[*Epzicom*] Abacavir plus Lamivudine
Adolescent (Weighing ≥25 kg) and Adult Dose:

- 1 tablet once daily

[*Triumeq*] Abacavir plus Dolutegravir plus Lamivudine
Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily

The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged ≥**3 years** with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 T lymphocyte count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily.

[a] Epivir HBV oral solution and tablets contain a lower amount of lamivudine than Epivir oral solution and tablets. The strength of lamivudine in Epivir HBV solution and tablet was based on dosing for treatment of hepatitis B virus (HBV) infection (in people without HIV coinfection). If Epivir HBV is used in HIV-infected patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen. The Epivir HBV tablet is appropriate for use in children who require a 100-mg lamivudine dose for treatment of HIV infection.

Stavudine (d4T, Zerit) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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, 40 mg

Dosing Recommendations

Neonate/Infant Dose (Birth to 13 Days):

- 0.5 mg/kg per dose twice daily

Pediatric Dose (Aged ≥14 Days and Weight <30 kg):

- 1 mg/kg per dose twice daily

Adolescent (≥30 kg)/Adult Dose:

- 30 mg per dose twice daily

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors). The risk is increased when used in combination with didanosine.
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- 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.

Tenofovir Alafenamide (TAF) (Last updated April 26, 2016; last reviewed April 26, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Fixed-Dose Combination Tablets

- *[Descovy]* Emtricitabine 200 mg plus tenofovir alafenamide (TAF) 25 mg
- *[Genvoya]* Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg
- *[Odefsey]* Emtricitabine 200 mg plus rilpivirine 25 mg plus TAF 25 mg

Dosing Recommendations

Combination Tablets

[Descovy] Emtricitabine 200 mg plus AF 25 mg

Adolescent (Weighing >35 kg) and Adult Dose:

- 1 tablet once daily

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily with food in antiretroviral (ARV) treatment-naive patients or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA <50 copies/mL) and on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no ARV treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.

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 use of TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, in patients with HBV infection monitor hepatic function for several months after therapy with TAF is stopped.
- If using Genvoya please see the elvitegravir, emtricitabine, and cobicistat sections of the drug appendix for additional information.
- Use of Genvoya is not recommended with other ARV drugs.
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or protease inhibitors co-formulated with cobicistat.
- When using Odefsey refer to the rilpivirine section. Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).

Pharmacology

- TAF undergoes renal excretion.
- Dosing in patients with renal insufficiency: TAF-containing formulations are not recommended in patients with estimated creatinine clearance below 30 mL per minute.
- TAF-containing formulations do not require dosage adjustment in patients with mild or moderate hepatic impairment, but should not be used in patients with severe hepatic impairment because they have not been studied in that group.

Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 26, 2016; last reviewed April 26, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral Powder: 40 mg per 1 g of oral powder (1 level scoop = 1 g oral powder; supplied with dosing scoop)

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

Fixed-Dose Combination Tablets

- *[Truvada low strength tablet]*
  - Emtricitabine 100 mg plus tenofovir disoproxil fumarate (TDF) 150 mg
  - Emtricitabine 133 mg plus TDF 200 mg
  - Emtricitabine 167 mg plus TDF 250 mg
- *[Truvada tablet]* Emtricitabine 200 mg plus TDF 300 mg
- *[Atripla]* Efavirenz 600 mg plus emtricitabine 200 mg plus TDF 300 mg
- *[Complera]* Emtricitabine 200 mg plus rilpivirine 25 mg plus TDF 300 mg
- *[Stribild]* Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not Food and Drug Administration-approved or recommended for use in neonates/infants aged <2 years.

Pediatric Dose (Aged ≥2 Years to <12 Years)[a]:

- 8 mg/kg/dose once daily

TDF Oral Powder Dosing Table

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

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density[a]

Special Instructions

- Do not crush tablets; TDF oral powder formulation is available for patients unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix TDF oral powder in 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 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 antiretroviral (ARV) drugs contained in a combination tablet. For

TDF Tablet Dosing Table
(Aged ≥2 Years and Weighing ≥17 kg)

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

Adolescent (Weighing ≥35 kg)[a] and Adult Dose:

- TDF 300 mg once daily

Combination Tablets

[Truvada] Emtricitabine plus TDF

Truvada Tablets Dosing Table

Body Weight kg	**FTC/TDF Tablet** Once Daily
17 to <22	One FTC 100 mg/TDF 150 mg tablet
22 to <28	One FTC 133 mg/TDF 200 mg tablet
28 to <35	One FTC 167 mg/TDF 250 mg tablet
≥35 (Adolescent and Adult)	One FTC 200 mg/TDF 300 mg tablet

[Atripla] Efavirenz plus Emtricitabine plus TDF

Adolescent (Aged ≥12 years and Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily.

[Complera] Emtricitabine plus Rilpivirine plus TDF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily in treatment-naive adults with baseline viral load <100,000 copies/mL or virologically suppressed adults, with no history of virologic failure, resistance to rilpivirine and other ARV drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 400 calories.

[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

Adolescent (Weighing >35 kg and Tanner Stage 4 or 5) and Adult Dose:

- 1 tablet once daily in treatment-naive adults or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.
- Administer with food.

Atripla (administer without food) and Complera (administer with a meal of at least 400 calories), refer to efavirenz or rilpivirine special instructions, respectively.

- Measure serum creatinine and urine dipstick for protein and glucose before starting a TDF-containing regimen and monitor serum creatinine and urine dipstick for protein and glucose at intervals (see Table 12i) during continued therapy. Measure serum phosphate if clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir and cobicistat sections of the drug appendix for additional information.

Metabolism/Elimination

- Renal excretion
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function (creatinine clearance <50 mL/min). Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
- Atripla and Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring 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.
- Stribild should not be used in patients with severe hepatic impairment.

[a] See text for concerns about decreased BMD, especially in pre-pubertal patients and those in early puberty (Tanner Stages 1 and 2).

Zidovudine (ZDV, AZT, Retrovir) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg

Tablets: 300 mg

Syrup: 10 mg/mL

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

Generic Formulations: Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Fixed-Dose Combination Tablets:

- [*Combivir and generic*] Lamivudine 150 mg plus zidovudine 300 mg
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

Dosing Recommendations

Recommended Neonatal Dosing for Treatment of HIV Infection[a]	
Gestational Age (weeks)	**Zidovudine Oral Dosing:** • Twice-Daily Dosing **Note:** For infants unable to tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval.
≥35 weeks	**Birth to Age 4 Weeks:** • 4 mg/kg orally twice daily **Aged >4 Weeks:** • 12 mg/kg orally twice daily
≥30 to <35 weeks	**Birth to Age 2 Weeks:** • 2 mg/kg orally twice daily **Aged 2 Weeks to 6 to 8 Weeks:** • 3 mg/kg orally twice daily **Aged >6 to 8 Weeks:** • 12 mg/kg orally twice daily
<30 weeks	**Birth to Age 4 Weeks:** • 2 mg/kg orally twice daily **Aged 4 Weeks to 8 to 10 Weeks:** • 3 mg/kg orally twice daily **Aged >8 to 10 Weeks:** • 12 mg/kg orally twice daily

[a] For prevention of perinatal transmission see Perinatal Guidelines

Selected Adverse Events

- Bone marrow suppression: macrocytosis with or without anemia, neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy

Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, 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.
- For infants unable to tolerate oral agents, the intravenous dose for newborns should be reduced by 25% while maintaining the same dosing interval.

Infant/Child Dose (Age ≥35 Weeks Post-Conception and at Least 4 Weeks Post-Delivery):

Weight-Based Dosing

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

Note: Weight-based dosing table should be used for infants aged ≥35 weeks post-conception, at least 4 weeks post-delivery with body weight ≥4 kg.

Body Surface Area Dosing:

- Oral: 180–240 mg/m^2 body surface area every 12 hours

Adolescent (Aged ≥18 Years) and Adult Dose:

- 300 mg twice daily

[*Combivir and generic*] Lamivudine plus Zidovudine

Adolescent (Weight ≥30 kg) and Adult Dose:

- 1 tablet twice daily

[*Trizivir*] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weight ≥40 kg) and Adult Dose:

- 1 tablet twice daily

Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal insufficiency.
- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use fixed-dose combination products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min, on dialysis, or who have impaired hepatic function.

Efavirenz (EFV, Sustiva) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 50 mg, 200 mg

Tablets: 600 mg

Fixed-Dose Combination Tablets:

- [*Atripla*] Efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg

Dosing Recommendations

Neonatal Dose:

- Efavirenz is not approved for use in neonates.

Pediatric Dose:

Infants and Children Aged 3 Months to <3 Years and Weighing ≥3 kg:

- The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) recommends that efavirenz generally not be used in children aged 3 months to <3 years. If use of efavirenz is unavoidable due to the clinical situation, the Panel suggests the use of investigational doses of efavirenz in this age group. See text for investigational dosing tables; evaluation of CYP 2B6 genotype is required prior to use. Therapeutic drug monitoring is recommended with an efavirenz concentration measured 2 weeks after initiation; some experts would also measure at age 3 years when making the dose adjustment. For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

Children Aged ≥3 Years and Weighing ≥10 kg:

Administer Efavirenz Once Daily

Weight (kg)	Efavirenz Dose (mg)[a,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

[a] The dose in mg can be dispensed in any combination of capsule strengths.

[b] Some experts recommend a dose of 367 mg/m^2 body surface area (maximum dose 600 mg) because of concern for under-dosing, especially at the upper end of each weight band (see Pediatric Use for details).

Selected Adverse Events

- Rash
- Central nervous system symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures, suicidality
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Potentially teratogenic
- Lipohypertrophy, although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors

Special Instructions

- Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Administer whole capsule or tablet of Atripla on an empty stomach. Avoid administration with a high-fat meal because of potential for increased absorption.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.
- Efavirenz should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Instructions for Use of Capsule as a Sprinkle Preparation with Food or Formula:

- Hold capsule horizontally over a small container and carefully twist to open to avoid spillage.

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 600 mg once daily

[*Atripla*] Efavirenz plus Emtricitabine plus TDF

- Atripla should not be used in pediatric patients <40 kg where the efavirenz dose would be excessive.

Adult Dose:

- One tablet once daily

- Gently mix capsule contents with 1–2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt), or reconstituted infant formula at room temperature.
- Administer infant formula mixture using a 10-mL syringe.
- After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Metabolism/Elimination

- Cytochrome P450 3A (CYP3A) and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Dosing of efavirenz in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product and TDF and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers at higher risk of toxicity (see text for information about therapeutic drug monitoring for management of mild or moderate toxicity).

Etravirine (ETR, Intelence, TMC 125) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 25 mg, 100 mg, and 200 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years (and Weighing ≥16 kg)

Body Weight Kilogram (kg)	Dose
16 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
≥30 kg	200 mg twice daily

Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.
- Diarrhea

Special Instructions

- Always administer etravirine following a meal. Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
- Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow etravirine tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 mL (1 teaspoon) of water, or enough liquid to cover the medication, and stir well until the water looks milky. If desired, add more water or alternatively orange juice or milk. **Note:** Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm (>40°C) drinks, or carbonated beverages should be avoided. Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

- Dosing of etravirine in patients with renal impairment: Dose adjustment is not required in patients with renal impairment.

Metabolism/Elimination

- Etravirine is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple interactions with antiretroviral agents and other drugs (see text below)

Nevirapine (NVP, Viramune) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg

Suspension: 10 mg/mL

Generic Formulations:

Tablets: immediate-release 200 mg, extended-release (ER) 400 mg only

Suspension: 10 mg/mL

Dosing Recommendations

Neonate/Infant Dose (≤14 Days) for Prevention:

- See Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States for dosing.

Treatment of HIV Infection:

Pediatric Dose: Immediate Release and Suspension Formulations

- <1 month: **Investigational dose** not Food and Drug Administration approved
- 34–37 weeks gestational age (no lead in): 4 mg/kg/dose twice daily for the first week increasing to 6 mg/kg/dose twice daily thereafter
- ≥37 weeks gestational age <1 month: 6 mg/kg/dose twice daily (no lead in) (See Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants)

≥1 Month to <8 years:

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

≥8 Years:

- 120–150 mg/m^2 BSA/dose twice daily after lead-in dosing (Maximum dose of immediate-release tablets is 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 is left static to achieve the appropriate mg-per-m^2 dosage as the child grows, as long as there are no untoward effects.[a]

Selected Adverse Events

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

Special Instructions

- Shake suspension well before administering and store at room temperature.
- Can be given without regard to food.
- Nevirapine-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 dose until rash resolves (see Major Toxicities section).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for more than 14 days, nevirapine dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement).
- Most cases of nevirapine-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).

Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine

BSA Range (m^2)	NVP XR (mg)
0.58–0.83	200 mg once daily (2 x 100 mg)
0.84–1.16	300 mg once daily (3 x 100 mg)
≥1.17	400 mg once daily (1 x 400 mg)

Pediatric Dose Extended-Release Formulation (>6 Years):

- Patients ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing.[a]

Adolescent/Adult Dose:

- 200 mg twice daily or 400 mg extended release once daily.

Nevirapine in Combination with Lopinavir/Ritonavir:

A higher dose of ritonavir-boosted lopinavir may be needed (see Ritonavir-Boosted Lopinavir section).

(glucuronidated metabolites).

- Dosing of nevirapine in patients with renal failure receiving hemodialysis: An additional dose of nevirapine should be given following dialysis.
- Dosing of nevirapine in patients with hepatic impairment: Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

* **Note:** Nevirapine is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose of the immediate-release formulation once daily (half-daily dose) for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate full dose, administered once daily, of the extended-release preparation. However, in children aged ≤2 years, some experts initiate nevirapine without a lead-in (see Dosing Considerations: Lead-In Requirement). In patients already receiving full-dose immediate-release nevirapine, extended release tablets can be used without the 200-mg lead-in period. Patients must swallow nevirapine extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of nevirapine at the same time. Dose should not exceed 400 mg daily.

Rilpivirine (RPV, Edurant) (Last updated April 26, 2016; last reviewed April 26, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 25 mg

Fixed-Dose Combination Tablet:

- [*Complera*] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [*Odefsey*] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir alafenamide (TAF) 25 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Children Aged <12 Years:

- Not approved for use in children aged <12 years.

Adolescent (Weighing ≥35 kg) and Adult Dose:

Antiretroviral-Naive Patients with HIV RNA ≤100,000 copies/mL or Virologically-Suppressed (HIV RNA <50 copies/mL) Patients with No History of Virologic Failure or Resistance to Rilpivirine and Other Antiretroviral (ARV) Drugs and Currently on Their First or Second Regimen:

- 25 mg once daily

Combination Tablet

[Complera] Emtricitabine plus Rilpivirine plus TDF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily in treatment-naive patients with baseline viral load <100,000 copies/mL or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Complera, and currently on their first or second regimen.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

Adolescent (Weighing ≥35 kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])
- Hepatotoxicity

Special Instructions

- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Antacids should only be taken either at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug with a known risk of *torsades de pointes* (see https://www.crediblemeds.org/).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Odefsey.

- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.
- When using Complera see the TDF section; when using Odefsey see the TAF section.

Atazanavir (ATV, Reyataz) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Powder Packet: 50 mg/packet

Capsules: 150 mg, 200 mg, and 300 mg

Fixed-Dose Combination Tablets

- *[Evotaz]* Atazanavir 300 mg plus Cobicistat 150 mg

Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates and infants younger than 3 months. Atazanavir should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric Dose

Powder Formulation:[a]

- Powder formulation must be administered with ritonavir.
- Not approved for use in infants younger than 3 months or weighing less than 5 kg.

Infants and Children (Aged ≥3 Months; Weighing ≥5 kg):

Atazanavir Powder[a]

Weight (kg)	Once-Daily Dose
5 to <15 kg	Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food
15 to <25 kg[b]	Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

Capsule Formulation:[a]

- Not approved for use in children <6 years or <15 kg

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with ritonavir boosting)

Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets are not interchangeable.
- Do not open capsules.
- Powder Administration:
  - Mix atazanavir oral powder with at least 1 tablespoon of food such as applesauce or 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 (<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 given using an oral dosing syringe.

Children (≥6 to <18 Years; Weight ≥15 kg):

Atazanavir Capsules[a]

Weight (kg)	Once-Daily Dose
<15 kg	Capsules not recommended
15 to <20 kg	Atazanavir 150 mg plus ritonavir[c] 100 mg, both once daily with food
20 to <40 kg[d]	Atazanavir 200 mg plus ritonavir[c] 100 mg, both once daily with food
≥40 kg	Atazanavir 300 mg plus ritonavir[c] 100 mg, both once daily with food

For Treatment-Naive Pediatric Patients who do not Tolerate Ritonavir:

- Atazanavir powder must be administered with ritonavir.
- For capsule formulation, atazanavir/ritonavir (ATV/r) is preferred for children and adolescents. Current Food-and-Drug-Administration-approved prescribing information does not recommend unboosted atazanavir in children aged <13 years. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see Pediatric Use).
- Only ATV/r should be used in combination with tenofovir disoproxil fumarate (TDF) because TDF decreases atazanavir exposure.

Adolescent (Aged ≥18 to 21 Years) and Adult Dose

Antiretroviral-Naive Patients:

- Atazanavir 300 mg plus ritonavir 100 mg once daily with food.[e]
- Atazanavir 300 mg plus cobicistat[f] 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.
- Atazanavir 400 mg once daily with food (if unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations [see Pediatric Use]).

Antiretroviral-Experienced Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.[e]
- Administer ritonavir immediately following powder administration.
- Administer the entire dosage of oral powder within 1 hour of preparation.
- Because atazanavir can prolong the ECG PR interval, use atazanavir with caution in patients with preexisting cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, special dosing information is indicated (see Drug Interactions for recommendations on dosing atazanavir when the drug is co-administered with H2 receptor antagonists). When administered with buffered didanosine formulations or antacids, give atazanavir at least 2 hours before or 1 hour after antacid or didanosine administration.
- The plasma concentration, and therefore therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is co-administered with proton-pump inhibitors. Antiretroviral therapy-naive patients receiving proton-pump inhibitors (PPIs) should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted atazanavir. Co-administration of atazanavir with PPIs is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.
- Atazanavir oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet contains 35 mg of phenylalanine.

Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).
- Dosing of atazanavir in patients with hepatic impairment: Atazanavir should be used with

- Atazanavir 300 mg plus cobicistat[f] 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.

Atazanavir in Combination with Efavirenz (Adults) in Treatment-Naive Patients Only:

- Atazanavir 400 mg plus ritonavir 100 mg plus efavirenz 600 mg, all once daily at separate times.[e]
- Although ATV/r should be taken with food, efavirenz should be taken on an empty stomach, preferably at bedtime. Efavirenz should not be co-administered with atazanavir (with or without ritonavir) in treatment-experienced patients because efavirenz decreases atazanavir exposure.

Atazanavir in Combination with TDF (Adults):

- Atazanavir 300 mg plus ritonavir 100 mg plus TDF 300 mg, all once daily with food.[e]
- Atazanavir 300 mg plus cobicistat[f] 150 mg plus TDF 300 mg, all once daily with food. Cobicistat is currently not recommended for use in children aged <18 years. Under investigation for children and youth aged 12 to 18 years.
- Only boosted atazanavir should be used in combination with TDF because TDF decreases atazanavir exposure.

caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. Atazanavir should not be used in patients with severe hepatic impairment.

- Dosing of atazanavir in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, atazanavir should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

[a] mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability is higher for the capsules than for the powder when studied in adults.

[b] For a child who cannot swallow atazanavir capsules and who weighs ≥ 25 kg, 300 mg (6 packets) atazanavir powder plus ritonavir oral solution 100 mg, both once daily with food, may be used.

[c] Either ritonavir capsules or ritonavir oral solution can be used.

[d] Some experts would increase atazanavir to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with TDF (see text for discussion).

[e] For adult patients who cannot swallow capsules, atazanavir oral powder is taken once daily with food at the same adult dosage as the capsules along with ritonavir.

[f] See Cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

Darunavir (DRV, Prezista) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral suspension: 100 mg/mL

Tablets: 75 mg, 150 mg, 400 mg, 600 mg, and 800 mg

Fixed-Dose Combination Tablets

- [*Prezcobix*] Darunavir 800 mg plus 150 mg Cobicistat

Dosing Recommendations

Note: Darunavir should not be used without a pharmacokinetic (PK) enhancer (boosting agent): ritonavir (children and adults) or cobicistat (adults only).

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose

Aged <3 years:

- **Do not use darunavir in children aged <3 years or weighing ≤10 kg** because of concerns related to seizures and death in infant rats due to immaturity of the blood-brain barrier and liver metabolic pathways.

Aged ≥3 years:

- See table below for children aged ≥3 years who are antiretroviral **treatment-naive and treatment-experienced** with or without one or more darunavir resistance-associated mutations.

Aged 3 to <12 Years and Weighing ≥10 kg

Weight (kg)	Dose (**Twice** daily with food)
10 to <11 kg[a]	darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 to <12 kg[a]	darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL[b])
12 to <13 kg[a]	darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL[b])
13 to <14 kg[a]	darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL[b])
14 to <15 kg	darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL[b])
15 to <30 kg	darunavir 375 mg (combination of tablets or 3.8 mL[c]) plus ritonavir 48 mg (0.6 mL[b])
30 to <40 kg	darunavir 450 mg (combination of tablets or 4.6 mL[c]) plus ritonavir 100 mg (tablet or 1.25 mL[b])
≥40 kg	darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- In patients with one or more darunavir-associated mutation(s), darunavir should only be used twice daily. **Darunavir resistance-associated mutations are**: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- Darunavir must be administered with food, which increases area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- Darunavir contains a sulfonamide moiety. The potential for cross sensitivity between darunavir and other drugs in the sulfonamide class is unknown. Use darunavir with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses depending on weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important.
- Store darunavir tablets at room temperature (25° C or 77° F).

[a] Note that the dose in children weighing 10 to 15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

[b] Ritonavir 80 mg/mL oral solution

[c] The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; however, the PK, efficacy, and safety of darunavir/cobicistat is currently under investigation in children aged 12 to 18 years.

Adolescent (Aged ≥12 Years and Weighing ≥30 kg) and Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance- Associated Mutations)

30 to <40 kg:

- Darunavir 675 mg (combination of tablets) plus ritonavir 100 mg **once daily**

≥40 kg:

- Darunavir 800 mg (tablet or combination of tablets) plus ritonavir 100 mg **once daily**

Adult Dose (Treatment-Naive or Treatment-Experienced with no Darunavir Resistance-Associated Mutations):

- Darunavir 800 mg (tablet) plus cobicistat[d] 150 mg (tablet) or coformulated as Prezcobix **once daily with food**

[d] See cobicistat section for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg; Treatment-Experienced with at Least One Darunavir Resistance-Associated Mutation):

- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

Adolescent (Aged ≥12 Years and Weighing ≥40 kg) and Adult Dose (Treatment-Experienced with at Least One Darunavir Resistance-Associated Mutation):

- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat **is not recommended** with darunavir 600 mg twice daily.
- Store oral suspension in the original container at room temperature (25° C or 77° F) and shake well before dosing.

Metabolism/Elimination

- Cytochrome (CYP) P450 3A4 inhibitor and substrate.

Dosing in Patients with Hepatic Impairment:

- Darunavir is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering darunavir to such patients. Darunavir is not recommended in patients with severe hepatic impairment.

Dosing in Patients with Renal Impairment:

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min). There are no PK data in patients with severe renal impairment or end-stage renal disease.

Fosamprenavir (FPV, Lexiva) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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 HIV-Infected Children (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants ≥4 weeks and for treatment-experienced infants ≥6 months; however, the Panel does not recommend use in infants younger than 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.

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

Aged ≥6 Months to 18 Years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients ≥6 Months Using Lexiva Oral Suspension with Ritonavir

Weight	Dose Fosamprenavir Plus Ritonavir Both twice daily[a] 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
≥20 kg	fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose

[a] 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 or buffered formulations of didanosine should take fosamprenavir at least 1 hour before or after antacid or didanosine 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 P450 3A4 (CYP3A4) 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 ≥39 kg. Ritonavir pills can be used in patients weighing ≥33 kg.

Adolescent and Adult (Aged >18 Years) Dose:

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

ARV-Naive Patients

Boosted with Ritonavir, Twice-Daily Regimen:

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

Boosted with Ritonavir, Once-Daily Regimen:

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

Protease Inhibitor (PI)-Experienced Patients:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.
- **Note:** Once-daily administration of fosamprenavir plus ritonavir is not recommended.

Fosamprenavir in Combination with Efavirenz (Adult):

- Only fosamprenavir boosted with ritonavir should be used in combination with efavirenz.

Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily plus efavirenz 600 mg once daily.

PI-Naive Patients Only, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 300 mg plus efavirenz 600 mg, all once daily.

- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

Indinavir (IDV, Crixivan) (Last updated February 12, 2014; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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^2 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

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- When 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).
- If co-administered with didanosine, give indinavir and didanosine ≥1 hour apart on an empty stomach.
- 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
- Dosing in patients with hepatic impairment: Decreased dosage should be used 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.

Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric Oral Solution: 80 mg/20 mg LPV/r per mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

Film-Coated Tablets: 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

Dosing Recommendations

Neonatal Dose (<14 Days):

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities.

Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

Infant Dose (14 Days–12 Months):

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area twice daily (approximates 16 mg/4 mg lopinavir/ritonavir per kg body weight twice daily). **Note:** This dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m^2 dose).

Pediatric Dose (>12 Months to 18 Years):

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (maximum dose 400 mg/100 mg lopinavir/ritonavir twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg lopinavir/ritonavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg lopinavir/ritonavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding in patients with hemophilia
- 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

- Lopinavir/ritonavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- Lopinavir/ritonavir tablets must be swallowed whole. Do not crush or split tablets.
- Lopinavir/ritonavir oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of lopinavir/ritonavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- Lopinavir/ritonavir oral solution can be kept at room temperature up to 77° F (25° C) if used within 2 months. If kept refrigerated (2° to 8° C or 36° to 46° F) lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label.

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

Weight-Band Dosing for 100 mg/25 mg Lopinavir/Ritonavir Pediatric Tablets for Children/Adolescents

	Recommended Number of 100-mg/25-mg Lopinavir/Ritonavir Tablets Given Twice Daily	
Dosing target	300 mg/m^2/dose given twice daily	230 mg/m^2/dose given twice daily
Body Weight (kg)		
15 to 20 kg	2	2
>20 to 25 kg	3	2
>25 to 30 kg	3	3
>30 to 35 kg	4[a]	3
>35 to 45 kg	4[a]	4[a]
>45 kg	4[a] or 5[b]	4[a]

[a] Four of the 100 mg/25 mg lopinavir/ritonavir tablets can be substituted with 2 tablets each containing 200 mg/50 mg lopinavir/ritonavir in children capable of swallowing a larger tablet.

[b] In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, for body weight >45 kg, the Food and Drug Administration (FDA)-approved adult dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing.

Adult Dose (>18 Years):

- 800 mg/200 mg lopinavir/ritonavir once daily, **or**
- 400 mg/100 mg lopinavir/ritonavir twice daily.
- Do **not** use once-daily dosing in children or adolescents, or in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special
- Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.
- Use of lopinavir/ritonavir once daily is specifically contraindicated if three or more of the following lopinavir 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—because higher lopinavir trough concentrations may be required to suppress resistant virus.

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 inhibitor and substrate.
- Dosing of lopinavir/ritonavir in patients with hepatic impairment: Lopinavir/ritonavir is primarily metabolized by the liver. Caution should be used when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the co-formulation of lopinavir/ritonavir, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.

Instructions for list).

In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):

- 400 mg/100 mg lopinavir/ritonavir twice daily.

Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:

Note: These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased lopinavir/ritonavir dosing is required with concomitant administration of these drugs.

- Once-daily dosing should **not** be used.

Pediatric Dose (>12 Months to 18 Years):

- 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult Dose (>18 Years):

- FDA-approved dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing. Once-daily dosing should **not** be used.

Lopinavir/Ritonavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:

- Saquinavir (SQV) and Maraviroc (MVC) doses may need modification (see sections on SQV and MVC).

Nelfinavir (NFV, Viracept) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/Infant Dose:

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

Pediatric Dose (Aged 2–13 Years):

- 45–55 mg/kg twice daily

Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily
- Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- 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, patients should 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

- CYP2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

Saquinavir (SQV, Invirase) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 200 mg

Tablets: 500 mg

Dosing Recommendations

Neonate and Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

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

Investigational Doses in Treatment-Experienced Children:

- Saquinavir must be boosted with ritonavir.

Aged <2 Years:

- No dose has been determined.

Aged ≥2 Years (Conditional Dosing Based on Limited Data; See Text):

Weight (kg)	Dose Saquinavir plus Ritonavir
5 to <15 kg	saquinavir 50 mg/kg plus ritonavir 3 mg/kg, both twice daily
15 to <40 kg	saquinavir 50 mg/kg plus ritonavir 2.5 mg/kg, both twice daily
≥40 kg	saquinavir 50 mg/kg plus ritonavir 100 mg, both twice daily

Adolescent (Aged ≥16 years) and Adult Dose:

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

Cobicistat is not interchangeable with ritonavir to increase systemic exposure of saquinavir. Saquinavir is not recommended for use in combination with cobicistat.

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Increased bleeding episodes in patients with hemophilia
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (torsades de pointes) have been reported.

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 and saquinavir is contraindicated in patients with a prolonged QT interval.

Metabolism/Elimination

- Cytochrome P (CYP) 450 3A4 and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: use with caution.

Tipranavir (TPV, APTIVUS) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

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

Capsules: 250 mg

Dosing Recommendations

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

Pediatric Dose (Aged <2 Years):

- Not approved for use in children aged <2 years.

Pediatric Dose (Aged 2–18 Years):

Note: Not recommended for treatment-naive patients

Body Surface Area Dosing:

- Tipranavir 375 mg/m^2 plus ritonavir 150 mg/m^2, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

Weight-Based Dosing:

- Tipranavir 14 mg/kg plus ritonavir 6 mg/kg, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

Adult Dose:

Note: Not recommended for treatment-naive patients

- Tipranavir 500 mg (two 250-mg capsules) plus ritonavir 200 mg, both twice daily

Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash (more common in children than adults)
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer tipranavir and ritonavir together with food.
- Tipranavir oral solution contains 116 IU vitamin E/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 bottle is 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;
- Dosing in patients with renal impairment: No dose adjustment required
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

Enfuvirtide (T-20, Fuzeon) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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.

Maraviroc (MVC, Selzentry) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 150 mg and 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children aged <18 years.
- A pediatric clinical trial is under way.

Adult Dose

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (except tipranavir/ritonavir [TPV/r]) and elvitegravir/ritonavir	150 mg twice daily
When given with nucleoside reverse transcriptase inhibitors, enfuvirtide, TPV/r, nevirapine, raltegravir, and drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor)	600 mg twice daily

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Orthostatic hypotension (especially in patients with severe renal insufficiency)

Special Instructions

- Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines) before using maraviroc to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use maraviroc in patients with only CCR5-tropic virus. Do not use if CXCR4 or mixed/dual-tropic HIV is present.
- Maraviroc can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering maraviroc to patients with underlying cardiac disease.

Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate
- Dosing of maraviroc in patients with hepatic impairment: Use caution when administering maraviroc to patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations may be increased in patients with hepatic impairment.

- Do not use maraviroc in patients with creatinine clearance <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.
- Dosing of maraviroc in patients with renal impairment: Refer to the manufacturer's prescribing information.

Dolutegravir (DTG, Tivicay) (Last updated Sept. 8, 2016; last reviewed Sept. 8, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 10 mg, 25 mg, and 50 mg

Fixed-Dose Combination Tablet:

- [*Triumeq*] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants

Children Weighing ≥30 to <40 kg:

- Not FDA approved for use in children weighing <30 kg.
- A clinical trial in ARV treatment-experienced (but INSTI-naive children) weighing <30 kg is underway (see text).

Body weight (kg)	Dose[a] (mg/day)	Tablet Number	Dosing Frequency	Tablet Size (mg)
>40	50	1	Once daily	50
30 to <40	35	2	Once daily	10 plus 25

[a] These doses are for children who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1/CYP3A inducers

Note: When ordering dolutegravir 10 mg or 25 mg tablets have the pharmacy call their drug wholesaler and tell the drug wholesaler to order directly from the GSK distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

Children and Adolescents (Weighing ≥40 kg) and Adult Dose:

Population	Recommended Dose
Treatment-naive or treatment-experienced/(INSTI)-naive	50 mg once daily
Treatment-naive or treatment-experienced/ INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a]	50 mg twice daily

[a] Combinations that do not include metabolic inducers should be considered where possible.

Selected Adverse Events

- Insomnia
- Headache
- Hypersensitivity reactions including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported rarely.

Special Instructions

- May be taken without regard to meals
- 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
- The efficacy of 50 mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).

Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of lack of data, dolutegravir is not recommended in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.

Combination Tablet
[Triumeq] Abacavir plus Dolutegravir plus Lamivudine:

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily
- For use in patients who are ARV treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min) because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

Elvitegravir (EVG, VITEKTA) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablet: 85 mg and 150 mg

Fixed-Dose Combination Tablets:

- [*Stribild*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil (TDF) 300 mg
- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 10 mg

Dosing Recommendations

Note: Elvitegravir should only be used with a pharmacokinetic (PK) enhancer (boosting agent) such as ritonavir as part of a boosted protease inhibitor (PI)-containing regimen, or in combination with cobicistat in Stribild or Genvoya.

Pediatric Dose (Weighing <35 kg):

- No data on appropriate dose of elvitegravir as Vitekta or in Stribild or Genvoya in children with body weight <35 kg.

Adolescent (Weighing > 35 kg) and Adult Dose:

Genvoya (Any Sexual Maturity Rating; Tanner Stage):[a]

- One tablet once daily

Stribild (SMR 4 or 5)[a]*:*

- One tablet once daily
- Elvitegravir (as Vitekta) in combination with an HIV PI co-administered with ritonavir and another antiretroviral (ARV) drug.[b]

Recommended Elvitegravir Dose Taken Once Daily with Food (All Drugs Administered Orally)

Dosage of EVG	Dosage of Concomitant PI	Dosage of Concomitant Ritonavir
85 mg once daily	Atazanavir 300 mg once daily	100 mg once daily
	Lopinavir 400 mg twice daily	100 mg twice daily
150 mg once daily	Darunavir 600 mg twice daily	100 mg twice daily
	Fosamprenavir 700 mg twice daily	100 mg twice daily
	Tipranavir 500 mg twice daily	200 mg twice daily

Selected Adverse Events

- Diarrhea (elvitegravir)
- Stribild-associated adverse events: Nausea, diarrhea, fatigue, headache. TDF—renal insufficiency, decreased bone mineral density, flatulence; cobicistat—alteration in tubular secretion of creatinine.
- Genvoya-associated adverse events: Nausea, diarrhea, fatigue, headache.
- TAF-associated adverse events: Increased low-density lipoprotein-cholesterol and total cholesterol.
- Cobicistat-associated adverse events: Alteration in tubular secretion of creatinine.

Special Instructions

- Administer with food.
- When used in combination with TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy; in patients at risk of renal impairment, also monitor serum phosphate. Patients with increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF is discontinued; therefore, monitor hepatic function for several months after therapy with emtricitabine, TDF, or TAF is stopped.
- Do not use elvitegravir with PIs co-administered with cobicistat (not yet studied), or with other elvitegravir-containing drugs

including Stribild or Genvoya. Neither Stribild nor Genvoya is recommended for use with other ARV drugs.

Metabolism/Elimination

- Elvitegravir is metabolized by cytochrome P (CYP) 450 3A4 and is a modest inducer of CYP2C9.
- Elvitegravir should only be used with a PK enhancer (boosting agent) such as ritonavir as part of a boosted PI-containing regimen or in combination with cobicistat (in Stribild or Genvoya). Refer to those sections for further details.
- Stribild should not be initiated in patients with estimated creatinine clearance <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min because dose adjustments required for FTC and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl <30 mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

[a] Stribild and Genvoya are Food and Drug Association (FDA)-approved for use in ARV treatment-naive adults or to replace the current ARV regimen in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild or Genvoya.

[b] Elvitegravir as Vitekta is not FDA-approved for use in children aged <18 years. The PK profile is similar to that in adults when given with either atazanavir/ritonavir or lopinavir/ritonavir, or darunavir/ritonavir. Vitekta was well tolerated in adolescents, but the use of a multi-pill regimen was associated with poor adherence and a high percentage of virologic failures, leading to the recommendation for use in adolescents only when elvitegravir is part of a coformulated regimen like Stribild or Genvoya.

Raltegravir (RAL, Isentress) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 400 mg (film-coated poloxamer tablet)
Chewable Tablets: 100 mg (scored) and 25 mg
Granules for Oral Suspension: Single-use packet of 100 mg

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

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates.
- **Note:** Metabolism by uridine diphosphate glucotransferase (UGT1A1) is immature in neonates. Neonatal dose is being studied.

Infant and Pediatric Dose

Oral Suspension Dosing Table[a]

Children Aged ≥4 Weeks and Weighing ≥3 kg to <20 kg:

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
3 to <4	1 mL (20 mg) twice daily
4 to <6	1.5 mL (30 mg) twice daily
6 to <8	2 mL (40 mg) twice daily
8 to <11	3 mL (60 mg) twice daily
11 to <14	4 mL (80 mg) twice daily
14 to <20	5 mL (100 mg) twice daily

[a] The weight-based dosing recommendation for the oral suspension is based on approximately 6 mg/kg/dose twice daily.

Note: Maximum dose of oral suspension is 5 mL (100 mg) twice daily.

Children Aged 2 to <12 Years:

- <25 kg: Chewable tablet twice daily (maximum of 300 mg twice daily). See table below for chewable tablet dose.
- ≥25 kg: 400-mg film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

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

- Can be given without regard to food.
- Avoid taking aluminum and/or magnesium containing antacids.
- Chewable tablets can be chewed or swallowed whole.
- 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 preparations.
- Chewable tablets should be stored in the original package with desiccant to protect from moisture.
- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided with a kit that includes two mixing cups, two dosing syringes, and 60 foil packets. Detailed

Chewable Tablet Dosing Table

Dosing[a] of Chewable Tablets in Children Aged 2 to <12 Years:

Body Weight (kg)	Dose	Number of Chewable Tablets
11 to <14	75 mg twice daily	3 X 25 mg twice daily
14 to <20	100 mg twice daily	1 X 100 mg twice daily
20 to <28	150 mg twice daily	1.5 X 100 mg[b] twice daily
28 to <40	200 mg twice daily	2 X 100 mg twice daily
≥40	300 mg twice daily	3 X 100 mg twice daily

[a] The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

[b] The 100-mg chewable tablet can be divided into equal halves.

Note: Maximum dose of chewable tablets is 300 mg twice daily.

Adolescent (Aged ≥12 Years) and Adult Dose:

- 400-mg film-coated tablet twice daily

instructions are provided in the Instructions for Use document. Each foil, single-use packet contains 100 mg of raltegravir, which will be suspended in 5 mL of water for final concentration of 20 mg/mL. Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document.

Metabolism/Elimination

- UGT1A1-mediated glucuronidation
- Dosing of raltegravir in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of raltegravir in patients with renal impairment: No dosage adjustment necessary

Cobicistat (COBI, TYBOST) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 150 mg

Fixed-Dose Combination Tablets:

- [*Stribild*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg
- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TAF 10 mg
- [*Evotaz*] Atazanavir 300 mg plus cobicistat 150 mg
- [*Prezcobix*] Darunavir 800 mg plus cobicistat 150 mg

Dosing Recommendations

Cobicistat is a Pharmacokinetic (PK) Enhancer:

- The only use of cobicistat is in adolescents and adults as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and the integrase inhibitor elvitegravir. Cobicistat is **not** interchangeable with ritonavir. See dosing information for specific PIs and elvitegravir that require cobicistat for boosting.

Pediatric Dosing

Not Food and Drug Administration (FDA)-Approved for Use in Children Aged <18 years:

- Cobicistat alone (as Tybost)
- Stribild
- Evotaz
- Prezcobix

Not FDA-Approved for Use in Children Aged <12 Years or Weighing <35 kg:

- Genvoya

Adolescent and Weighing ≥35 kg

- Cobicistat 150 mg orally once daily as a component of Genvoya

Adult (Aged ≥18 Years) Dose:

- Cobicistat must be administered as
  - The combination tablet Stribild or Genvoya, in which case it would not be dosed with any other antiretroviral (ARV) drugs; *or*
  - The tablet Tybost co-administered with atazanavir or darunavir at the doses listed in the table below and at the same time, in combination with other ARV drugs; *or*
  - Combination tablets with atazanavir (Evotaz) or darunavir (Prezcobix), with food, and in

Selected Adverse Events

- When co-administered with TDF, cobicistat may be associated with higher risk of renal tubular adverse events than ritonavir.

Special Instructions

- Cobicistat is not interchangeable with ritonavir.
- Do not administer cobicistat with ritonavir or with drugs containing cobicistat.
- Not recommended for use with more than one ARV that requires PK enhancement (e.g., elvitegravir in combination with a PI) because no data are available.
- Use with PIs other than atazanavir 300 mg or darunavir 800 mg administered once daily is not recommended because no data are available on other combinations or doses.
- Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety.
- When used in combinations with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see Table 12i). In patients at risk of renal impairment, also monitor serum phosphate.
- When used in combination with other ARV drugs, see those specific sections of the appendix (atazanavir, darunavir, elvitegravir, TDF, TAF).

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor
- Cobicistat inhibits renal tubular secretion of

combination with other ARV drugs.

Cobicistat Dose	Co-administered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild or Genvoya; no other ARV drugs needed	Treatment-naive or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya
150 mg orally once daily	Atazanavir 300 mg (co-formulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (co-formulated as Prezcobix or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced with no darunavir-associated resistance mutations

creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

Dosing of Cobicistat in Patients with Renal Impairment:

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl <30 mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

Ritonavir (RTV, Norvir) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral Solution (Contains 43% Alcohol by Volume): 80 mg/mL

Capsules: 100 mg

Tablets: 100 mg

Dosing Recommendations

Ritonavir as a Pharmacokinetic (PK) Enhancer[a]:

- Ritonavir is used as a PK enhancer of other protease inhibitors (PIs) and of an integrase inhibitor (elvitegravir) when elvitegravir is included in a boosted, protease-containing regimen. The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs and for elvitegravir.

[a] **Note:** Ritonavir has antiviral activity but is not used as an antiviral agent (see text).

Selected Adverse Events

- Gastrointestinal intolerance, nausea, vomiting, diarrhea
- Paresthesia (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

Special Instructions

- Administer ritonavir with food to increase absorption and reduce gastrointestinal adverse effects.
- Do not administer ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild).
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- Refrigerate ritonavir capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). Ritonavir tablets are heat stable.
- Do **not** refrigerate ritonavir oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- Ritonavir oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is

smaller than the capsule and thus easier to swallow.

- To Increase Tolerability of Ritonavir Oral Solution in Children:
  - Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
  - Before administration, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.
  - After administration, give a child strong-tasting foods such as maple syrup or cheese.
  - Check food allergy history before making these recommendations.

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- Dosing of ritonavir in patients with hepatic impairment: Ritonavir is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.