



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen)

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)

Combination Tablets:

- With lamivudine (3TC): ABC 600 mg + 3TC 300 mg (Epzicom)
- With zidovudine (ZDV) and 3TC: ABC 300 mg + ZDV 300 mg + 3TC 150 mg (Trizivir)

Dosing Recommendations

Neonate/infant dose:

ABC is not approved for infants <3 months of age.

Pediatric dose:

Oral solution (>3 months of age):

8 mg/kg (maximum 300 mg) twice daily.

In clinically stable patients with undetectable viral load and stable CD4 cell count, may consider using once-daily ABC dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see [Pediatric Use](#)).

Scored 300-mg tablet (body weight ≥ 14 kg):

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	PM Dose	Total Daily Dose
14–21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥ 30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (≥ 16 years of age)/adult dose:

300 mg twice daily or 600 mg once daily.

Trizivir

Adolescent (body weight ≥ 40 kg)/adult dose:

One tablet twice daily.

Epzicom

Adolescent (≥ 16 years of age)/adult dose:

One tablet once daily.

Selected Adverse Events

- Hypersensitivity reaction (HSR) that may be fatal; symptoms may include fever; rash; nausea; vomiting; malaise or fatigue; loss of appetite; respiratory symptoms such as sore throat, cough, shortness of breath.
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; 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 hypersensitivity; patients with the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.
- ABC can be given without regard to food.
- Caution patients and parents about the risk of serious, potentially fatal HSR. Do not rechallenge.

Metabolism

- Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%.
- ABC requires dosage adjustment in hepatic insufficiency. Do not use Trizivir and Epzicom (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Didanosine (ddl, Videx)

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

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 ddl delayed-release capsules: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/infant dose (2 weeks to <3 months of age):

50 mg/m² of body surface area every 12 hours.

(Manufacturer recommends 100 mg/m² of body surface area every 12 hours in this age range. Panel members interpret pharmacokinetic [PK] data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m² of body surface area every 12 hours.)

Infant dose (>3 months to 8 months of age):

100 mg/m² of body surface area every 12 hours.

Pediatric dose of oral solution (>8 months of age):

120 mg/m² of body surface area every 12 hours. (Dose range: 90–150 mg/m² of body surface area every 12 hours, maximum dose 200 mg/dose twice daily.)

Pediatric dose of Videx EC or generic capsules (ages 6–18 years and body weight ≥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

In treatment-naïve children 3–21 years of age, 240 mg/m² of body surface area once daily (oral solution or capsules) has been used with effective viral suppression.

Selected Adverse Events

- Peripheral neuropathy
- Electrolyte abnormalities
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in adults. (The risk is increased when ddl is used in combination with stavudine [d4T].)
- Pancreatitis (less common in children than in adults, more common in adults when ddl is used in combination with tenofovir [TDF] or d4T)
- Potential association with noncirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddl, it is generally recommended to administer ddl on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer ddl without regard to timing of meals (see Pediatric Use).
- ddl oral solution contains antacids that may interfere with the absorption of other medications.
- Shake ddl oral solution well before use. Keep refrigerated; admixture is stable for 30 days.

Metabolism

- Renal excretion 50%.

Adolescent/adult dose:

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

ddl in combination with TDF:

This combination should be avoided if possible because of enhanced ddl toxicity.

Pediatric/adolescent dose of ddl when combined with TDF:

There is no data on this combination in children or adolescents <18 years of age, but decrease in ddl dose is recommended as in adults.

Adult dose of ddl 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

- **Dosing of ddl 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 (CrCl).

Emtricitabine (FTC, Emtriva)

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

Combination tablets:

- With *tenofovir (TDF)*: FTC 200 mg + TDF 300 mg (Truvada)
- With *TDF and efavirenz (EFV)*: FTC 200 mg + TDF 300 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose (0–3 months of age):

Oral solution: 3 mg/kg once daily.

Pediatric dose (≥3 months–17 years of age):

Oral solution:

6 mg/kg (maximum dose 240 mg) once daily.

Capsules (for children who weigh >33 kg):

200 mg once daily.

Adolescent (≥18 years of age)/adult dose:

Oral solution: 240 mg (24 mL) once daily.

Capsules: 200 mg once daily.

Combination Tablets

Truvada (FTC + TDF)

Adult dose: 1 tablet once daily.

Atripla (FTC + TDF + EFV)

Adult dose: 1 tablet once daily.

See *efavirenz* section for pregnancy warning.

Selected Adverse Events

- Minimal toxicity.
- Severe acute exacerbation of hepatitis can occur in hepatitis B virus (HBV)-coinfected patients who discontinue FTC.
- Hyperpigmentation/skin discoloration on palms and/or soles, predominantly observed in nonwhite patients.

Special Instructions

- FTC can be given without regard to food; however, administer Atripla on an empty stomach because it also contains EFV.
- FTC oral solution can be kept at room temperatures up to 77°F (25°C) if used within 3 months; refrigerate for longer term storage.
- Before using FTC, screen patients for HBV.

Metabolism

- Limited metabolism: No cytochrome P (CYP)450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- **Dosing of FTC 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.

Lamivudine (3TC/Epivir)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Oral Solution: 10 mg/mL (Epivir); 5 mg/mL (Epivir HBV*)

Tablets: 150 mg (scored) and 300 mg (Epivir); 100 mg (Epivir HBV*)

Combination Tablets:

- *With zidovudine (ZDV):* 3TC 150 mg + ZDV 300 mg (Combivir)
- *With abacavir (ABC):* 3TC 300 mg + ABC 600 mg (Epzicom)
- *With ZDV and ABC:* 3TC 150 mg + ZDV 300 mg + ABC 300 mg (Trizivir)

* Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The formulation and dosing of 3TC in Epivir HBV was **maximized for the treatment of hepatitis B virus (HBV) only. 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 3TC dose for treatment of HIV infection.**

Dosing Recommendations

Epivir (oral solution and tablets)

Neonate/infant dose (age <4 weeks) for prevention of transmission or treatment:

2 mg/kg twice daily.

Pediatric dose (age ≥4 weeks):

4 mg/kg (maximum dose 150 mg) twice daily.

Pediatric dosing for scored 150-mg tablet (body weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose (mg)
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (age ≥16 years)/adult dose:

Body weight <50 kg:

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

Body weight ≥50 kg:

150 mg twice daily or 300 mg once daily.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic hepatitis B infection.

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before **administering 3TC.**

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Combivir

Adolescent (body weight ≥ 30 kg)/adult dose:
1 tablet twice daily.

Trizivir

Adolescent (body weight >40 kg)/adult dose:
1 tablet twice daily.

Epzicom

Adolescent (age >16 years and body weight >50 kg)/adult dose:
1 tablet once daily.

Stavudine (d4T, Zerit)

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

Formulations

Oral Solution: 1 mg/mL

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

Generic: d4T capsules and solution have been approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/infant dose (birth to 13 days):
0.5 mg/kg twice daily.

Pediatric dose (14 days and body weight <30 kg):
1 mg/kg twice daily.

Adolescent (body weight \geq 30 kg)/adult dose:
30 to <60 kg: 30 mg twice daily.
 \geq 60 kg: 40 mg twice daily*.

* The World Health Organization (WHO) recommends 30 mg twice daily regardless of body weight in adults (see [Pediatric Use](#)).

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 [NRTIs])
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- d4T can be given without regard to food.
- Shake d4T oral solution well before use. Keep refrigerated; the solution will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

Tenofovir Disoproxil Fumarate (TDF, Viread)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Tablet: 300 mg

Combination tablets:

- With *emtricitabine* (FTC): TDF 300 mg + FTC 200 mg (Truvada)
- With FTC + *efavirenz* (EFV): TDF 300 mg + FTC 200 mg + EFV 600 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

TDF is not approved for use in neonates/infants.

Pediatric dose*:

TDF is not approved for use in children <12 years of age. Investigational doses of 210 mg/m² body surface area (range 175 to 300 mg/m²) have been used once daily in children <12 years of age.

Adolescent (≥12 years of age and body weight >35 kg) dose*:

300 mg once daily

*See [Pediatric Use](#) for concerns about decreased bone mineral density (BMD), especially in prepubertal patients and those in early puberty (Tanner Stages 1 and 2).

Combination Tablets

Adult dose: 300 mg once daily.

Truvada (TDF + FTC)

Adult dose: 1 tablet once daily.

Atripla (TDF + FTC + EFV)

Adult dose: 1 tablet once daily.

TDF in combination with didanosine (ddl):

The combination of TDF and ddl should be avoided if possible. If used, ddl dose requires modification. See section on ddl.

TDF in combination with atazanavir (ATV):

When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased BMD

Special Instructions

- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. Because Atripla also contains EFV, the combination tablet should be administered on an empty stomach.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV can occur when TDF is discontinued; therefore, monitor hepatic function for several months after therapy with TDF is stopped.

Metabolism

- Renal excretion.
- **Dosing of ddl 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 (CrCl).
 - Atripla (fixed-dose combination) 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.

Zidovudine (ZDV, AZT, Retrovir)

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 infusion: 10 mg/mL

Generic: ZDV capsules, tablets, and solution are approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Combination Tablets:

- With lamivudine (3TC): ZDV 300 mg + 3TC 150 mg (Combivir)
- With 3TC + abacavir (ABC): ZDV 300 mg + 3TC 150 mg + ABC 300 mg (Trizivir)

Dosing Recommendations

Dose for infant <35 weeks gestation for prevention of transmission or treatment (standard neonate dose may be excessive in premature infants):

1.5 mg/kg of body weight (intravenous) or 2 mg/kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates \geq 30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age).

(See [Perinatal Guidelines](#) for additional information.)

Neonate/infant dose (<6 weeks of age) for prevention of transmission or treatment:

Oral: 2 mg/kg of body weight every 6 hours.

Intravenous: 1.5 mg/kg of body weight every 6 hours.

(See [Perinatal Guidelines](#) for additional information.)

Pediatric dose (6 weeks to <18 years of age):

Body surface area dosing:

Oral: 180–240 mg/m² of body surface area every 12 hours or 160 mg/m² every 8 hours.

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or 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 ZDV without regard to food.
- If substantial granulocytopenia or anemia develop in patients receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells and platelets.

Metabolism

- Metabolized to AZT glucuronide (GAZT), which is renally excreted.

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

**Three times daily dosing is approved but rarely used in clinical practice.*

Adolescent (≥18 years of age)/adult dose:

300 mg twice daily.

Combivir (ZDV + 3TC)

Adolescent (weight ≥30 kg)/adult dose:
1 tablet twice daily.

Trizivir (ZDV + 3TC + ABC)

Adolescent (weight ≥40 kg)/adult dose:
1 tablet twice daily.

- **Dosing of ZDV in patients with renal impairment:** Dosage adjustment is required in renal insufficiency.
- **Dosing of ZDV in patients with hepatic impairment:** Decreased dosing may be required in patients with hepatic impairment.
- Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Efavirenz (EFV, Sustiva)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Capsules: 50 mg and 200 mg

Tablets: 600 mg

Combination Tablets:

- With *emtricitabine (FTC)* and *tenofovir disoproxil fumarate (TDF)*:
EFV 600 mg + FTC 200 mg + TDF 300 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

EFV is not approved for use in neonates/infants.

Pediatric dose:

Children <3 years of age:

No data are currently available on the appropriate EFV dosage for children <3 years of age.

Children ≥3 years and body weight ≥10 kg:
Administer EFV once daily:

Weight (kg)	EFV Dose (mg)*†
10 to <15	200
15 to <20	250
20 to <25	300
25 to <32.5	350
32.5 to <40	400
≥40	600

* The dose in mg can be dispensed in any combination of capsule strengths.

† Some experts recommend a dose of 367 mg/m² of body surface area (maximum dose of 600 mg) because of concern for underdosing, especially at the upper end of each weight band (see Pediatric Use for details).

Adolescent (body weight ≥40 kg)/adult dose:
600 mg once daily.

Atripla (EFV + FTC + TDF)

Atripla should not be used in pediatric patients

Selected Adverse Events

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

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. Avoid administration with a high-fat meal because of potential for increased absorption.
- Administer Atripla on an empty stomach.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- EFV should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).
- CYP3A4 and CYP2B6 substrate.
- **Dosing of EFV in patients with hepatic**

<40 kg where the EFV dose would be excessive.

Adult dose: One tablet once daily.

EFV in combination with other antiretroviral (ARV) drugs:

Dosage adjustment or the addition of ritonavir (RTV) may be necessary when EFV is used in combination with atazanavir (ATV), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).

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, it should not be used in patients with creatinine clearance (CrCl) of <50 mL/minute or in patients on dialysis.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers having higher risk of toxicity. (See [Pediatric Use](#) for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

Etravirine (ETR, Intelence, TMC 125)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Tablets: 100 mg and 200 mg

Dosing Recommendations

Neonate/infant dose:

ETR is not approved for use in neonates/infants.

Pediatric (6-11 years of age) dose:

ETR is not approved for use in children. Investigational dose currently in Phase II trial is 5.2 mg/kg (maximum 200 mg) twice daily in children ≥ 6 years of age.

Adolescent (12-17 years of age) dose:

ETR is not approved for this age group. Preliminary data from the Phase II trial (5.2 mg/kg, maximum 200 mg, twice daily—see [Pediatric Use](#) section) showed lower exposure than adults.

Adult dose (antiretroviral [ARV]-experienced patients):

200 mg twice daily following a meal.

Selected Adverse Events

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

Special Instructions

- Always administer ETR following a meal. Area under the curve (AUC) of ETR is decreased by about 50% when the drug is taken on an empty stomach.
- ETR tablets are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in a small amount of water. Instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times, and each time the rinse water should be swallowed completely to ensure that the entire dose is consumed.
- **Dosing of ETR 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 ETR in patients with renal impairment:** Dose adjustment is not required in patients with renal impairment.

Metabolism

- Metabolism by cytochrome P450: inducer of cytochrome P450 3A4 (CYP3A4) and inhibitor of CYP2C9 and CYP2C19. Substrate for CYP3A4, 2C9, and 2C19. Also inhibitor of p-glycoprotein (Pgp).
- Multiple drug interactions (see below).

Nevirapine (NVP, Viramune)

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

Formulations

Tablets: 200 mg, extended release 400 mg

Suspension: 10 mg/mL

Dosing Recommendations

Neonate/infant dose:

Neonate/infant dose (age ≤ 14 days):

See [Perinatal Guidelines](#) for information on use of NVP for prophylaxis of mother-to-child transmission (MTCT) of HIV. Treatment dose is not defined for infants age ≤ 14 days.

Pediatric dose (age ≥ 15 days):

(See note below about initiation of therapy.)

Age <8 years:

200 mg/m² of body surface area/dose (maximum dose 200 mg) twice daily.

Age ≥ 8 years: 120–150 mg/m² of body surface area/dose (maximum dose 200 mg) twice daily.

When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m² dosage as the child grows, as long as there are no untoward effects.

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P (CYP) 450 metabolizing enzymes, which results in increased clearance of the drug. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily 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 dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/adult dose:

200 mg twice daily.

Note: Initiate therapy with 200 mg given once daily

Selected Adverse Events

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

Special Instructions

- NVP can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase NVP dose until rash resolves (see [Major Toxicities](#)).
- If NVP dosing is interrupted for more than 7 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests (LFTs), is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of LFTs is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have LFTs performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions (HSRs).
- Shake NVP suspension well and store at room temperature.

for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

400 mg extended release once daily (not approved for use in children).

Note: Initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg administered once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release NVP, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow NVP 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.

NVP in combination with lopinavir/ritonavir (LPV/r):
A higher dose of LPV/r may be needed. See LPV/r section.

Metabolism

- Metabolized by CYP450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- **Dosing of NVP in patients with renal failure receiving hemodialysis:** An additional dose of NVP should be given following dialysis.
- **Dosing of NVP in patients with hepatic impairment:** NVP should not be administered to patients with moderate or severe hepatic impairment.

Rilpivirine (Edurant, TMC 278)

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

Formulations

Tablet: 25 mg

Dosing Recommendations

Neonate/infant dose:

Rilpivirine is not approved for use in neonates/infants.

Pediatric dose:

Rilpivirine is not approved for use in children.

Adult dose (antiretroviral [ARV]-naive patients only):

25 mg once daily.

Selected Adverse Events

- Depression, mood changes
- Insomnia
- Headache
- Rash

Special Instructions

- Instruct patients to take rilpivirine with a meal.
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Use rilpivirine with caution when coadministered with a drug with a known risk of torsade de pointes (<http://www.qtdrugs.org/>).
- Use rilpivirine with caution in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism

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

Atazanavir (ATV, Reyataz)

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

Formulations

Capsules: 100 mg, 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/infant dose:

ATV is not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

Data are insufficient to recommend dosing of ATV in all children younger than 6 years or in treatment-experienced children who weigh less than 25 kg.

For children ≥ 6 to < 18 years of age:

Weight (kg)	Once-Daily Dose*
Treatment-Naive ** Children Only	
15 to < 25 kg	ATV 150 mg + RTV 80 mg, both once daily with food
Both Treatment Naive and Treatment-Experienced Children	
25 to < 32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32 to < 39 kg	ATV 250 mg + RTV 100 mg, both once daily with food
≥ 39 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Higher doses than those currently recommended may be required for some patients. See discussion under [Pediatric Use](#).

** Data are insufficient to recommend this dose in treatment-experienced children who weigh less than 25 kg.

*For treatment-naive pediatric patients who do not tolerate ritonavir (RTV): **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.***

Selected Adverse Events

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

Special Instructions

- Administer ATV with food to enhance absorption.
- Because ATV can prolong the electrocardiogram (ECG) PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated. (See [Drug Interactions](#) for recommendations on dosing ATV when the drug is coadministered with H2 receptor antagonists.) When administered with buffered didanosine (ddl) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddl administration.
- **The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is coadmin-**

Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children younger than 13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see [Pediatric Use](#)).

Adolescent (≥18–21 years of age)/adult dose:

Antiretroviral-naïve patients:

ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food. (If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see [Pediatric Use](#)].)

Antiretroviral-experienced patients:

ATV 300 mg + RTV 100 mg, both once daily with food.

ATV in combination with efavirenz (EFV) (adults) in therapy-naïve patients only:

ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily at separate times.

Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure.

ATV in combination with tenofovir (TDF) (adults):

ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food.

Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

istered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naïve patients receiving PPIs should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted ATV. Coadministration of ATV with PPIs is not recommended in treatment-experienced patients.

- Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and patients with marked elevations in transaminases prior to treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP)3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).
- **Dosing of ATV in patients with hepatic impairment:** ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- **Dosing of ATV in patients with renal impairment:** No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

Darunavir (DRV, Prezista)

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

Formulations

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

Dosing Recommendations

DRV should not be used without ritonavir (RTV).

Neonate/infant dose:

DRV is not approved for use in neonates/infants.

Pediatric dose:

DRV should not be used in pediatric patients <3 years of age.

3 to <6 years of age:

Safety and efficacy have not been established.

6 to <18 years of age and body weight ≥ 20 kg:

Weight (kg)	Dose DRV + RTV (both twice daily* with food)
≥ 20 to <30 kg	DRV 375 mg + RTV 50 mg (0.6 ml of 80 mg/ml) [†]
≥ 30 to <40 kg	DRV 450 mg + RTV 60 mg (0.8 ml of 80 mg/ml) [†]
≥ 40 kg	DRV 600 mg + RTV 100 mg

* Do not use once-daily dosing in children <12 years of age or in any patient <18 years of age who is treatment experienced. Once-daily dosing (DRV 800 mg + RTV 100 mg) may be used in treatment naive pediatric patients 12–18 years of age and body weight >40 kg (see [Pediatric Use](#)).

[†] To enhance palatability, RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation, even though the RTV dose is higher.

Adolescent (≥ 18 years of age)/adult dose (treatment naive or antiretroviral [ARV] experienced with no DRV mutations):

DRV 800 mg + RTV 100 mg, both once daily with food.

Selected Adverse Events

- Skin rash (DRV has a sulfonamide moiety. Stevens-Johnson syndrome [SJS] and erythema multiforme have been reported.)
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Administer DRV 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.
- DRV contains a sulfa moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store DRV at room temperature (25°C or 77°F).

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing in patients with hepatic impairment:** DRV is primarily metabolized by the liver. No

**Adolescent (≥ 18 years of age)/adult dose
(treatment experienced with at least one DRV
mutation):**

DRV 600 mg + RTV 100 mg, both twice daily with food.

data exist for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV 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). No pharmacokinetic (PK) data exist in patients with severe renal impairment or end-stage renal disease.

Fosamprenavir (FPV, Lexiva)

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

Formulations

Tablets: 700 mg FPV calcium

Oral suspension: 50 mg/mL

Dosing Recommendations

Neonate/infant dose:

Not approved for use in neonates/infants.

Pediatric dose (2–18 years of age):

Dosing regimen depends on whether patient is antiretroviral (ARV) naive or ARV experienced. Once-daily dosing is not recommended for pediatric patients.

ARV-naive patients (2–5 years of age):

Unboosted (without ritonavir [RTV]):
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily.

ARV-naive patients (>6–18 years of age):

Unboosted (without RTV):
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily.

or

Boosted with RTV:

FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily.

ARV-experienced patients (>6–18 years of age):

Boosted with RTV:
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily.

Note: When administered without RTV, the adult regimen of FPV tablets (FPV 1,400 mg twice daily) can be used for patients weighing ≥ 47 kg *or* when administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given twice daily, can be used in patients weighing ≥ 39 kg. RTV pills can be used in patients weighing ≥ 33 kg.

Adolescent (>18 years of age)/adult dose:

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

Selected Adverse Events

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

Special Instructions

- FPV tablets with RTV should be taken with food. FPV tablets without RTV can be taken with or without food. Pediatric patients should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take FPV at least 1 hour before or after antacid or ddI use.
- FPV contains a sulfonamide moiety. The potential for cross sensitivity between FPV and other drugs in the sulfonamide class is unknown. FPV should be used with caution in patients with sulfonamide allergy.
- Shake FPV oral suspension well prior to use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as FPV is absorbed.

ARV-naive patients:

Unboosted (without RTV), twice-daily regimen:

FPV 1,400 mg twice daily.

Boosted with RTV, twice-daily regimen:

FPV 700 mg + RTV 100 mg, both twice daily.

Boosted with RTV, once-daily regimen:

FPV 1,400 mg + RTV 100–200 mg, both once daily.

Protease inhibitor (PI)-experienced patients:

FPV 700 mg + RTV 100 mg, both twice daily.

Once-daily administration of FPV + RTV is not recommended in PI-experienced patients.

FPV in combination with efavirenz (EFV) (adults):

Only FPV boosted with RTV should be used in combination with EFV.

Twice-daily regimen:

FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily.

PI-naive patients only, once-daily regimen:

FPV 1,400 mg + RTV 300 mg + EFV 600 mg, all once daily.

FPV in combination with maraviroc (MVC) (adults):

See [MVC section](#) for dosing of FPV with MVC.

- APV is a cytochrome P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.
- **Dosing in patients with hepatic impairment:** Dosage adjustment is recommended.

Indinavir (IDV, Crixivan)

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/infant dose:

IDV is not approved for use in neonates/infants.

IDV should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

IDV is not approved for use in children.

A range of IDV doses (234–500 mg/m² of body surface area) boosted by low-dose ritonavir (RTV) has been studied in children (see [Pediatric Use](#)).

Adolescent/adult dose:

800 mg IDV + 100 or 200 mg RTV every 12 hours.

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal (GI) 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

- Administer IDV on an empty stomach 1 hour before or 2 hours after a meal (or administer with a light meal). When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If coadministered with didanosine (ddI), give IDV and ddI ≥1 hour apart on an empty stomach.
- IDV capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

Metabolism

- 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 IDV 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)

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/mL (contains 42.4% alcohol by volume)

Pediatric Tablets: 100 mg/25 mg LPV/r

Tablets: 200 mg/50 mg LPV/r

Dosing Recommendations

Neonate dose (age <14 days):

No data on appropriate dose or safety of LPV/r in this age group. Do not administer to neonates before a postmenstrual age of 42 weeks and a post-natal age of at least 14 days.

Infant dose (age 14 days–12 months) in individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV):

Once-daily dosing is **not** recommended.

The recommended dose of the oral solution is 300 mg/75 mg LPV/r per m² of body surface area **twice daily** or 16 mg/4 mg LPV/r per kg of body weight twice daily.

NOTE: Use of 300 mg/75 mg LPV/r per m² of body surface area in infants 12 months of age or younger is associated with lower LPV trough levels than those found in adults; in infants, LPV dosing should be adjusted for growth at frequent intervals (see [Pediatric Use](#)).

Pediatric dose (age >12 months–18 years) in individuals not receiving concomitant NVP, EFV, FPV, or NFV:

Once-daily dosing is **not** recommended.

Body surface area dosing:

230 mg/57.5 mg LPV/r/m² of body surface area per dose twice daily in antiretroviral (ARV)-naive patients older than age 1 year. For patients already receiving LPV/r, immediate dose reduction at age 12 months is not recommended: many practitioners would allow the patient to “grow into” the 230 mg/m² dosage as they gain weight over time (see [Pediatric Use](#)).

300 mg/75 mg LPV/r/m² of body surface area per dose twice daily is used by many clinicians, espe-

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 torsade de pointes
- **Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see [Major Toxicities](#)).**

Special Instructions

- LPV/r tablets can be administered without regard to food, but recognize that administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food. A high-fat meal increases absorption, especially of the liquid preparation.
- **The poor palatability of LPV/r oral solution can sometimes be partially masked with flavorings or foods (see [Pediatric Use](#)).**
- LPV/r 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°

cially for patients previously treated with ARV drugs (see [Pediatric Use](#)).

Weight-based dosing:

<15 kg: 12 mg/3 mg LPV/r per kg of body weight per dose twice daily.

≥15 kg to 40 kg: 10 mg/2.5 mg LPV/r per kg of body weight per dose twice daily.

≥40 kg: 400 mg/100 mg LPV/r per dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents Without Concomitant NVP, EFV, FPV, or NFV.

Body Weight (kg)	Body Surface Area (m ²)	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 25 kg	≥0.6 to <0.9 m ²	2
>25 to 35 kg	≥0.9 to <1.4 m ²	3
>35 kg	≥1.4 m ²	4 (or two 200 mg/50 mg LPV/r adult tablets)

Pediatric dose (age >12 months to 18 years) For individuals receiving concomitant NVP, EFV, FPV, or NFV.

(These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs and/or in treatment-experienced patients in whom reduced susceptibility to LPV is suspected, such as patients with prior treatment with other protease inhibitors [PIs].)

Do not administer LPV/r with NVP, EFV, FPV, or NFV in infants 6 months of age or younger.

Once-daily dosing is **not** recommended.

Body surface area dosing:

300 mg/75 mg LPV/r/ per m² of body surface area per dose twice daily.

Weight-based dosing:

<15 kg: 13 mg/3.25 mg LPV/r per kg of body weight per dose twice daily.

to 46°F) LPV/r oral solution remains stable until the expiration date printed on the label.

- LPV resistance-associated substitutions: LPV/r can be administered once daily (800 mg/200 mg) in adults with fewer than three LPV resistance-associated substitutions. Once-daily administration of LPV/r is not recommended for adult patients with three or more of the following LPV resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P 450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing of LPV/r in patients with hepatic impairment:** LPV/r is primarily metabolized by the liver. Caution should be used when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, the RTV acts as a pharmacokinetic (PK) enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

≥15 kg to 45 kg: 11 mg/2.75 mg LPV/r per kg of body weight per dose twice daily.

≥45 kg: Use adult dose twice daily.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children With Concomitant NVP, EFV, FPV, or NFV

Body Weight (kg)	Body Surface Area (m ²)	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 20 kg	≥0.6 to <0.8 m ²	2
>20 to 30 kg	≥0.8 to <1.2 m ²	3
>30 to 45 kg	≥1.2 to <1.7 m ²	4 (or two 200 mg/50 mg LPV/r tablets)
>45 kg	≥1.7 m ²	4 or 6 (or two 200 mg/50 mg LPV/r adult tablets)*

**The higher dose may be considered in treatment-experienced patients when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing.*

NOTE: In children, use of 230 mg/57.5 mg LPV/r per m² of body surface area (when not coadministered with NVP, EFV, FPV, or NFV) or use of 300 mg/75 mg LPV/r per m² of body surface area (when coadministered with NVP, EFV, FPV, or NFV) is associated with area under the curve (AUC) LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults. Therefore, some clinicians may choose to initiate therapy with higher doses of LPV/r when coadministered with these drugs or in PI-experienced pediatric patients who may have reduced PI susceptibility (see [Pediatric Use](#)).

Adult dose (age >18 years):

In patients with fewer than three LPV-associated mutations (see [Special Instructions](#) for list):

800 mg/200 mg LPV/r once daily; **or**

400 mg/100 mg LPV/r twice daily.

Do **not** use once-daily dosing in children or adolescents. Once-daily dosing should not be used in

patients receiving concomitant therapy with NVP, EFV, FPV, or NFV.

In patients with three or more LPV-associated mutations (see [Special Instructions](#) for list):

400 mg/100 mg LPV/r twice daily.

In patients receiving concomitant NVP, EFV, FPV, or NFV):

Food and Drug Administration (FDA)-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of two tablets of 200/50 mg LPV/r and one tablet of 100 mg/25 mg LPV/r. Most Panel members would use 600 mg/150 mg LPV/r for ease of dosing. Once-daily dosing should **not** be used.

LPV/r in combination with saquinavir (SQV) hard-gel capsules (Invirase) or in combination with maraviroc (MVC):

SQV and MVC doses may need modification. See [sections on SQV or MVC](#).

Nelfinavir (NFV, Viracept)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Powder for oral suspension: 50 mg/1 level gram scoopful (200 mg/1 level teaspoon)

(Oral powder contains 11.2 mg phenylalanine per gram of powder.)

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/infant dose:

NFV should not be used for treatment in children <2 years of age.

(See the [perinatal guidelines](#) for recommendations on use of NFV for prevention of mother-to-child transmission [PMTCT] of HIV.)

Pediatric dose (2–13 years of age):

45–55 mg/kg twice daily.

Adolescent/adult dose:

1,250 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 [TDM] 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 NFV with meal or light snack.
- If coadministered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- NFV powder for oral suspension may be mixed with water, milk, pudding, ice cream, or formula; **refrigerated** mixture is stable for up to 6 hours.
- Do not mix powder with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of NFV oral powder. The scoop provided with the powder should be used for measuring. The powder and solution should be mixed in another container.
- Patients unable to swallow NFV 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

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

Ritonavir (RTV, Norvir)

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

RTV as a pharmacokinetic (PK) enhancer:

The major use of RTV is as a PK enhancer of other protease inhibitors (PIs) **used in pediatric patients and in adolescents and adults.** The dose of RTV recommended varies **and is specific to the drug combination selected.** See dosing information for specific PIs.

In the unusual situation when RTV is prescribed as sole PI:

See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Paresthesias (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer RTV with food to increase absorption and reduce GI side effects.
- If RTV is prescribed with didanosine (ddI), administer the drugs 2 hours apart.
- Refrigerate RTV capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). RTV tablets are heat stable.
- Do not refrigerate RTV oral solution; store at room temperature (68–77°F or 20–25°C). Shake the solution well before use.
- RTV oral solution has limited shelf life; use within 6 months.

To increase tolerance of RTV oral solution in children:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.

- Before administration, give the child ice chips, a popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds or give the child peanut butter to coat the mouth.
- After administration, give the child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- **Dosing of RTV in patients with hepatic impairment:** RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are not available on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

Saquinavir (SQV, Invirase)

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

Formulations

Hard-gel capsules (HGC): 200 mg

Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/infant dose:

SQV is not approved for use in neonates/infants.

Pediatric dose:

SQV is not approved for use in children.

Investigational doses in treatment-experienced children:

SQV must be boosted with ritonavir (RTV):

<2 years of age:

No dose has been determined.

≥2 years of age (**conditional dosing based on limited data, see [Pediatric Use](#)**):

Weight (kg)	Dose SQV + RTV
5 to <15 kg	SQV 50 mg/kg + RTV 3 mg/kg, both twice daily
15 to 40 kg	SQV 50 mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50 mg/kg + RTV 100 mg, both twice daily

≥7 years of age in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (**conditional dosing based on limited data, see [Pediatric Use](#)**):

SQV 750 mg/m² (max 1,600 mg) or SQV 50 mg/kg have **been used in combination with** LPV/r, both twice daily.

Adolescent (≥16 years of age)/adult dose:

SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

SQV in combination with RTV:

SQV 1,000 mg + RTV 100 mg, both twice daily.

Selected Adverse Events

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

Special Instructions

- Administer SQV within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions in patients using SQV; advise patients to use sunscreen or protective clothing.
- **Pretherapy electrocardiogram (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval or in patients who are receiving other drugs that can prolong the QT interval.**

Metabolism

- **Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor**, 90% metabolized in the liver.
- **Use in patients with hepatic impairment:** Use with caution.

Tipranavir (TPV, APTIVUS)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Oral solution: 100 mg TPV/mL with 116 International Units (IU) vitamin E/mL

Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose used for TPV is higher than that used for other protease inhibitors (PIs).

Pediatric dose (<2 years of age):

TPV is not approved for use in children <2 years of age.

Pediatric dose (2–18 years of age):

Body surface area dosing:

TPV 375 mg/m² + RTV 150 mg/m², both twice daily.

Maximum dose:

TPV 500 mg + RTV 200 mg, both twice daily.

Weight-based dosing:

TPV 14 mg/kg + RTV 6 mg/kg, both twice daily.

Maximum dose:

TPV 500 mg + RTV 200 mg, both twice daily.

Adult dose:

TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily.

Selected Adverse Events

- Rare cases of fatal and nonfatal intracranial hemorrhage (ICH)
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer TPV with food.
- TPV oral solution contains 116 IU of vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- TPV contains a sulfonamide component and should be used with caution in patients with sulfonamide allergy.
- Store TPV 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 oral TPV capsules in a refrigerator at 2°–8°C (36°–46°F). Capsules can be kept at room temperature (maximum of 25°C or 77°F) if used within 2 months after the bottle is first opened.
- Use TPV with caution in patients who may be at risk of increased bleeding from trauma,

surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

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

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate.
- **Dosing of TPV in patients with renal impairment:** No dose adjustment is required.
- **Dosing of TPV in patients with hepatic impairment:** No dose adjustment is required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

Enfuvirtide (ENF, T-20, Fuzeon)

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 ENF. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience kit: 60 single-use vials of ENF (90-mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes

Dosing Recommendations

Pediatric/adolescent dose (6–16 years of age):

Children <6 years of age:

ENF is not approved for use in children <6 years of age.

Children ≥6 years of age:

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

Adolescent (>16 years of age)/adult dose:

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

Selected Adverse Events

- Local injection site reactions.
- 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 subcutaneous injections. ENF injection instructions are provided with convenience kits.
- After adding sterile water to vial of ENF, allow vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject ENF immediately or keep refrigerated in the original vial until use. Reconstituted ENF must be used within 24 hours.
- ENF must be given subcutaneously; severity of reactions increases if given intramuscularly.
- Give each injection of ENF 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 if alternative delivery systems, such as needle-free injection devices, are used.

- Advise patient/caregiver of the possibility of an HSR; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with an HSR.

Metabolism

- Catabolism to constituent amino acids.

Maraviroc (MVC, Selzentry)

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:

MVC is not approved for use in neonates/infants.

Pediatric dose:

MVC is not approved for use in children <16 years of age. A dose finding study is under way.

Adolescent (>16 years of age)/adult dose:

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including protease inhibitors (PIs) (except tipranavir/ritonavir [TPV/r])	150 mg twice daily
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When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide (ENF), TPV/r, nevirapine (NVP), raltegravir (RAL), and drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
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When given with potent CYP3A inducers including efavirenz (EFV) and etravirine (ETR) (without a potent CYP3A inhibitor)	600 mg twice daily
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Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity
- Orthostatic hypotension

Special Instructions

- Conduct testing with HIV tropism assay (see [Antiretroviral Drug-Resistance Testing](#) in the main body of the guidelines) before using MVC to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Use MVC in patients with only CCR5-tropic virus. Do not use if CXCR4 or mixed/dual-tropic HIV is present.
- Give MVC without regard to food.
- Instruct patients/caregivers on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) substrate.
 - **Dosing of MVC in patients with hepatic impairment:** Use caution when administering MVC to patients with hepatic impairment. Because MVC is metabolized by the liver, concentrations in patients with hepatic impairment may be increased.
- Do not use MVC in patients with creatinine clearance (CrCl) <30 mL/min who are receiving potent CYP3A4 inhibitors or inducers.

- **Dosing of MVC in patients with renal impairment:** Refer to the manufacturer's prescribing information.

Raltegravir (RAL, Isentress)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Tablets: 400 mg (poloxamer tablet)

Dosing Recommendations

Neonate/infant dose:

RAL is not approved for use in neonates/infants.

Pediatric dose:

RAL is not approved for use in children <16 years of age.

Investigational dose in children >6 years of age (and body weight >25 kg):

400 mg twice daily.

Adolescent (≥ 16 years of age)/adult dose:

400 mg twice daily.

Selected Adverse Events

- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Give RAL without regard to food.

Metabolism

- Uridine diphosphate glucotransferase (UGT1A1)-mediated glucuronidation.
- **Dosing of RAL 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 RAL in patients with renal impairment:** No dosage adjustment is necessary.