Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Stavudine (d4T, Zerit)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

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Abacavir (ABC, Ziagen) (Last updated August 11, 2011; last reviewed November 1, 2012)

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:

- Not approved for infants aged <3 months.

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 T lymphocyte count, can consider using once-daily abacavir dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see text).

Scored 300 mg tablet (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–<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 (aged ≥16 years)/adult dose:

- 300 mg twice daily or 600 mg once daily.

Trizivir

- *Adolescent (weight ≥40 kg)/adult dose:* One tablet twice daily.

Selected Adverse Events

- Hypersensitivity reaction 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 risk of serious HSR that can be fatal. Do not re-challenge.

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,

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Epzicom

- *Adolescent (≥16 years of age)/adult dose:* One tablet once daily.

patients on dialysis, or those with impaired hepatic function.

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Thus, it should not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors.
- Abacavir is metabolized by alcohol dehydrogenase and glucuronyl transferase. Alcohol increases abacavir levels by 41%.

Major Toxicities:

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups: (1) fever; (2) constitutional, including malaise, fatigue, or achiness; (3) gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain; or (4) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. If an HSR is suspected, abacavir should be stopped and **not restarted because hypotension and death have occurred upon re-challenge**. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis can occur.
- *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ABC.html).

Pediatric Use: Abacavir is Food and Drug Administration (FDA) approved for use in HIV-infected children as one of the drugs for part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The liquid formulation of abacavir is more palatable than zidovudine; it has less of an effect on mitochondrial function than zidovudine, stavudine, or didanosine; and it has more durable antiviral effectiveness in pediatric trials.[1, 2] The risk of abacavir hypersensitivity syndrome, the major toxicity limiting abacavir's use, is greatly reduced by testing patients for HLA-B*5701 and by not using abacavir in those who test positive for the HLA-B*5701 allele.

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that children

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have more rapid clearance of abacavir than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure.[3, 4] Metabolic clearance of abacavir in adolescents and young adults (ages 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.[5]

Plasma area under the drug concentration by time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.[6, 7] Intracellular concentrations of NRTIs are most strongly associated with antiviral effectiveness, and the active form of abacavir is the intracellular metabolite carbovir triphosphate.[8, 9] Measurement of intracellular carbovir triphosphate is more difficult than measurement of plasma AUC, so the abacavir plasma AUC is often taken as a proxy measurement for intracellular concentrations. However, this relationship is not sufficiently strong that changes in plasma AUC can be assumed to reflect true changes in intracellular active drug. For example, although overall intracellular carbovir triphosphate was correlated with abacavir plasma AUC, this relationship was not found when gender was considered in PK modeling[10] because carbovir triphosphate concentrations were higher in females than in males.[10-12] This effect of gender on intracellular triphosphates has also been found with zidovudine and lamivudine.[8, 13]

In studies in adults, abacavir plasma AUC is decreased 17% by concurrent use of atazanavir/ritonavir and decreased 32% by concurrent use of lopinavir/ritonavir.[14] In a study comparing PK parameters of abacavir in combination with either lopinavir/ritonavir or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of lopinavir/ritonavir, but the carbovir triphosphate concentration seemed to increase in the lopinavir/ritonavir group.[12]

These effects of gender and concurrent PI use add to the complexity of linking readily available plasma abacavir AUC with more difficult to obtain but pharmacodynamically more important intracellular carbovir triphosphate concentrations. These effects also need to be kept in mind when considering data supporting the use of once-daily abacavir in children (presented **in the table below**).

Abacavir 600 mg once daily is standard for use in adults, but once-daily use for children is still controversial. The PENTA-13 crossover trial studied abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in 24 children aged 2 to 13 years who had undetectable or low, stable viral loads at the time of changing from twice-daily to once-daily abacavir. This study showed equivalent AUC_{0-24} for both drugs and improved acceptability in the once-daily dosing arm.[15, 16] However, trough concentrations were lower in younger children (aged 2–6 years) receiving the once-daily regimen.[16] The PENTA-15 crossover trial studied 18 children aged 3 to 36 months, again comparing abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in children with viral loads <400 copies/mL or "stable" on twice-daily abacavir at baseline. AUC_{0-24} and clearance were similar on the once- and twice-daily regimens. After the change from twice-daily to once-daily abacavir, viral load remained <400 copies/mL in 16 of 18 participants through 48 weeks of monitoring.[17] A study of 41 children aged 3 to 6 years (median age 7.6 years) in Uganda who were stable on twice-daily abacavir also showed equivalent AUC_{0-24} and good clinical outcome (disease stage and CD4 T lymphocyte (CD4 cell) count) after the switch to once-daily abacavir, with median follow-up of 1.15 years. Viral load testing was not done.[18]

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Abacavir Steady State Pharmacokinetics When Dosed Once Daily or Twice Daily

Study/ (reference)	PENTA 15[17]		PENTA 13[16]		Arrow[18]		5		10	
Location	Europe		Europe		Uganda		U.S.		U.S.	
N	18		14		36		15	15	27	
Age (years)	2		5		7		16[a]	22[a]	45[a]	
Sex (% male)	56%		43%		42%		53%	53%	70%	
Race (% black or African American)	78%				100%		53%	60%	18%	
Body weight (kg)	11		19		19		63[a]	72[a]	NA	
Concurrent PI use	8		1		0		9	0	NA	
Dosing interval (hours)	12	24	12	24	12	24	12	12	12	24
Administered dose median (mg/kg) or fixed amount (mg)	8.04	16.02	8.1	16.4	19.6[c]	19.1	300[d]	300[d]	300[d]	600[d]
Administered dose range (mg/kg)	7.7-8.3[e]	15.5-16.3[e]	5.0-8.4	15.6-17.1	15.4-23.1[c]	14.6-23.1				
AUC_{0-24} (mg*hr/L)	10.85[b]	11.57[b]	9.91[b]	13.37[b]	15.6[b]	15.28[b]	7.01	6.59	7.90[b]	8.52[b]
C_{max} (mg/L)	1.38[b]	4.68[b]	2.14[b]	4.80[b]	4.18[b]	6.84[b]	2.58	2.74	1.84[b]	3.85[b]
C_{min} (mg/L)	0.03[b]	<0.015[b]	0.025[b]	<0.015[b]	0.021[b]	0.006[b]				
Cl/F/kg (L/hr/kg)	1.47[b]	1.38[b]	1.58[b]	1.16[b]	1.23[b]	1.24[b]	9.80[f]	12.10[f]		
Carbovir-triphosphate AUC_{0-24}(h*fmol/10^6 cells)							530[g]	315[g]	814	1,051

Key to Abbreviations: AUC = area under the curve, PI = protease inhibitor

Data are medians except as noted.

[a] mean
[b] geometric mean
[c] total daily dose in mg/kg (divided doses were given but sometimes in unequal amounts morning and evening)
[d] total dose in mg
[e] interquartile range
[f] clearance in mL/min/kg
[g] AUC in fmol/10^6 cells

No clinical trials exist involving children who initiated ART with once-daily dosing of abacavir. All three pediatric studies described in the table above enrolled only patients who had low viral loads or were "clinically stable" on twice-daily abacavir before changing to once-daily dosing. Therefore, the Panel suggests that in clinically stable patients with undetectable viral loads and stable CD4 cell counts, switching to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose to maximum of 600 mg once daily) can be considered.

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Didanosine (ddI, Videx) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Dosing Recommendations

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

Infant dose (aged ≥3 months to 8 months):

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

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

- 120 mg/m^2 of body surface area every 12 hours.

  (Dose range: 90–150 mg/m^2 of body surface area every 12 hours; maximum dose 200 mg/dose twice daily.)

Pediatric dose of Videx EC or generic capsules (aged 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-naive children aged 3–21 years, 240 mg/m^2 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 ddI is used in combination with stavudine [d4T].)
- Pancreatitis (less common in children than in adults, more common in adults when ddI is used in combination with tenofovir [TDF] or d4T)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Because food decreases absorption of ddI, administration of ddI on an empty stomach (30 minutes before or 2 hours after a meal) generally is recommended. To improve adherence, some practitioners administer ddI without regard to timing of meals (see text below).
- ddI oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual protease inhibitor for instructions on timing of administration. This interaction is more pronounced for the buffered (solution) formulation of ddI, than for the enteric coated formulation.

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Adolescent/adult dose:

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

ddI in combination with TDF:

- This combination should be avoided, if possible, because of enhanced ddI toxicity.

Pediatric/adolescent dose of ddI when combined with TDF:

- No data on this combination in children or adolescents aged <18 years, but decrease in ddI dose is recommended as in adults.

Adult dose of ddI 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

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

Metabolism

- Renal excretion 50%.
- Dosing of ddI 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Absorption:* The presence of antacids in didanosine suspension has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by timing doses to avoid giving other medications concurrently with didanosine suspension.
- *Mechanism unknown:* Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir and this combination should be avoided if possible.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* Risk of pancreatitis and peripheral neuropathy is increased with use of some nucleoside reverse transcriptase inhibitors (NRTIs) (such as stavudine). The combination of stavudine and didanosine is not recommended (unless the benefits clearly outweigh the risks) because of overlapping toxicities and reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

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Pancreatitis (less common in children than in adults, more common in adults when used in combination with tenofovir or stavudine), increased liver enzymes, and retinal depigmentation and optic neuritis have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefit clearly outweighs the potential risk.

- *Rare:* Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use in adults.[1-3] In adults, use of didanosine may be associated with increased risk of myocardial infarction.[4]

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ddI.html).

Pediatric Use: Didanosine is Food and Drug Administration (FDA) approved for use in children as part of a dual-NRTI backbone in combination antiretroviral therapy (cART).

Recommended doses of didanosine oral solution in children have traditionally been 90 to 150 mg/m^2 body surface area per dose twice daily. Doses higher than 180 mg/m^2 body surface area twice daily are associated with increased toxicity.[5] The pharmacokinetic (PK) variable of greatest pharmacodynamic significance is the area under the curve (AUC), with virologic response best when didanosine AUC $\geq$0.60 mg*h/L.[6, 7] In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg/m^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with adequate exposure predicted in 88% of patients at a dose of 120 mg/m^2 body surface area twice daily,[7] which is the currently recommended dose for children aged 8 months to 3 years.

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m^2 body surface area per dose twice daily, increasing to 120 mg/m^2 body surface area per dose twice daily at age 8 months. However, 2 small studies suggest that a higher AUC is seen in infants aged <6 weeks and that a dose of 100 mg/m^2 body surface area per day (either as 50 mg/m^2 body surface area per dose twice daily or 100 mg/m^2 body surface area once daily) in infants aged <6 weeks achieves AUCs consistent with those for higher doses in older children.[8, 9] Therefore, because these PK differences in younger infants (aged 2 weeks–3 months) compared with older children raise concern for increased toxicity in that age group, the Panel recommends a dose of 50 mg/m^2 of body surface area twice daily for infants younger than 3 months.

A once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing. In a study of 10 children aged 4 to 10 years, EC didanosine (Videx EC) administered as a single dose of 240 mg/m^2 body surface area once daily was shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine.[8] The resultant intracellular (active) drug concentrations are unknown. In 24 HIV-infected children, didanosine oral solution at a dose of 180 mg/m^2 body surface area once daily was compared with 90 mg/m^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group.[10] Long-term virologic suppression with a once-daily regimen of efavirenz, emtricitabine, and didanosine (oral solution or EC beadlet capsules) was reported in 37 treatment-naive children aged 3 to 21 years.[11] The didanosine dose used in that study was 240 mg/m^2/dose once daily, and PK analysis showed no dose changes were needed to reach PK targets.[11] A European trial of once-daily combination therapy in 36 children aged 3 to 11 years that included didanosine at a dose of 200 to 240 mg/m^2 body surface area demonstrated safety and efficacy with up to 96 weeks of follow up.[12] In 53

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children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg/m^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was less in the children given once-daily therapy.[13] In 51 children (median age 6.0 years, range 2.5 to 15.0 years) in Burkina Faso, the once-daily combination of didanosine-lamivudine-efavirenz resulted in week-48 viral load <300 copies/mL in 81% of treated participants. That study used didanosine at a dose of 240 mg/m^2/day, administered in the fasting state as tablets with a separate antacid (not enteric-coated capsules).[6]

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and it may decrease medication adherence by increasing regimen complexity. A comparison showed that regardless of whether didanosine oral solution was given to children with or without food systemic exposure measured by AUC was similar; absorption of didanosine administered with food was slower and elimination more prolonged.[14] To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food.[15, 16] A European study dosed didanosine oral solution as part of a four-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction, and showed good virologic outcome with up to 96 weeks of follow-up.[17]

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Emtricitabine (FTC, Emtriva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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):* 200 mg FTC + 300 mg TDF (Truvada)
- *With TDF and efavirenz (EFV):* 200 mg FTC + 300 mg TDF + 600 mg EFV (Atripla)
- *With TDF and rilpivirine (RPV):* 200 mg FTC + 300 mg TDF + 25 mg RPV (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose (aged 0–<3 months):

- *Oral solution:* 3 mg/kg once daily.

Pediatric dose (aged ≥3 months–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 (for children who weigh >33 kg):* 200 mg once daily.

Adolescent (aged ≥18 years)/adult dose:

- *Oral solution:* 240 mg (24 mL) once daily.
- *Capsules:* 200 mg once daily.

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and ≥40 kg) and adult dose:* 1 tablet once daily.
- See efavirenz section for pregnancy warning.

Complera

- *Adult dose (aged ≥18 years):* 1 tablet once daily.

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.

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 temperature 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

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Stribild: • *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food.	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. • If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Do not use emtricitabine in combination with lamivudine because the agents share similar resistance profiles and lack additive benefit.
- *Renal elimination:* Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance.
- *Use with Stribild:* If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Major Toxicities:

- *More common:* Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children).
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in HIV/hepatitis B virus-co-infected patients who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/FTC.html).

Pediatric Use: Emtricitabine is Food and Drug Administration (FDA)-approved for once-daily administration in children starting at birth. Owing to its once-a-day dosing, minimal toxicity, and pediatric pharmacokinetic (PK) data, emtricitabine is commonly used as part of a dual-NRTI backbone in antiretroviral therapy (ART).

A single-dose PK study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children ages 2 to 17 years.[1] Emtricitabine was found to be well absorbed following oral administration,

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with a mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg emtricitabine once-daily dose were approximately equivalent to those in adults receiving the standard 200-mg dose.

Based on this dose-finding study, emtricitabine was given at a dose of 6 mg/kg once daily in combination with other antiretroviral (ARV) drugs.[2, 3] PK results were similar to the preceding dose-finding study.[1] Follow-up data extending to Week 96 indicated that 89% of the ARV-naive and 76% of the ARV-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (74% of ARV-naive children and 62% of ARV-experienced children at <50 copies/mL). Minimal toxicity was observed in this trial.

In PACTG P1021, emtricitabine at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with didanosine and efavirenz, all given once daily, was studied in 37 ARV-naive HIV-infected children aged 3 months to 21 years.[2] Eighty-five percent of children achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm^3 at Week 96.

A study in South Africa evaluated the PKs of emtricitabine in 20 HIV-exposed infants aged <3 months, given emtricitabine as 3 mg/kg once daily for two, 4-day courses, separated by an interval of ≥2 weeks.[4] Emtricitabine exposure (area under the curve [AUC]) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients aged >3 months receiving the recommended emtricitabine dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200-mg emtricitabine dose (AUC approximately 10 hr*ug/mL). Over the first 3 months of life, emtricitabine AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (N = 6) receiving a single dose of emtricitabine 3 mg/kg after a single maternal dose of 600 mg during delivery, the AUC exceeded that seen in adults and older children, but the half-life (9.2 hrs) was similar.[5] Extensive safety data are lacking in this age range.

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Lamivudine (3TC/Epivir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 HBVa)

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

Combination tablets:

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

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The strength of 3TC in Epivir HBV solution and tablet was maximized for 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

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 (up to 150 mg) twice daily.

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

Weight (kg)	AM dose	PM dose	Total Daily Dose
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21–<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:*
  150 mg twice daily or 300 mg once daily.
- *Body weight <50 kg:*
  4 mg/kg (up to 150 mg) twice 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

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Combivir

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

Trizivir

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

Epzicom

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

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit.[1]

Major Toxicities:

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

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/3TC.html).

Pediatric Use: Lamivudine is Food and Drug Administration (FDA)-approved for use in children aged ≥3 months, and it is a common component of most nucleoside backbone regimens.

Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral (ARV) drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response.[2-17] Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone.[3, 4, 6, 7, 11, 12, 14, 16, 17] In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.[18] Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150 mg scored tablets.[19, 20]

Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.[11] A population pharmacokinetic (PK) analysis of infants receiving lamivudine affirms that adjusting the dose of lamivudine from 2 mg/kg to 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure.[21] For infants in the first 2 weeks of life, weight-band dosing has also been used. In HPTN 040, all infants weighing >2000 g received 6 mg twice daily and infants weighing ≤2000 g received 4 mg twice daily for 2 weeks. These doses resulted in similar lamivudine exposure as in infants

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receiving the standard 2 mg/kg/dose twice daily dosing schedule for neonates.[22]

The standard adult dosage for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of 8 mg/kg leads to area under the curve $(AUC)_{0-24}$ values similar to 4 mg/kg twice daily but C_{min} values significantly lower and C_{max} values significantly higher in children ages 1 to 18 years.[23] Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children ages 2 to 13 years in the PENTA-13 trial[2] and in children 3 to 36 months of age in the PENTA 15 trial.[24] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC_{0-24} and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children ages 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC_{0-24} and good clinical outcome (disease stage and CD4 T lymphocyte [CD4 cell] count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years.[25] All three studies enrolled only patients who had low viral load or were clinically stable on twice-daily lamivudine before changing to once-daily dosing. Nacro et al studied a once-daily regimen in ARV-naive children in Burkina-Faso composed of non-enteric-coated didanosine (ddI), lamivudine, and efavirenz. Fifty-one children ranging in age from 30 months to 15 years were enrolled in this open-label, Phase II study lasting 12 months.[26] The patients had advanced HIV infection with a mean CD4 percentage of 9 and a median plasma RNA of 5.51 log_{10}/copies/mL. At 12-month follow-up, 50% of patients had a plasma RNA <50 copies/mL and 80% were <300 copies/mL with marked improvements in CD4 percentage. Twenty-two percent of patients harbored multi-class-resistant viral strains. While PK values were similar to the PENTA and ARROW trials, the study was complicated by use of non-enteric-coated ddI, severe immunosuppression, and non-clade B virus. In addition, rates of virologic failure and resistance profiles were not separated by age. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged 3 years and older with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 cell count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of lamivudine can be used effectively to initiate antiretroviral therapy in children.

Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine

Study/(reference)	PENTA 15[24]		PENTA 13[2]		ARROW[25]	
	Europe		Europe		Uganda	
N	17		14		35	
	2		5		7	
Sex (% male)	56%		43%		42%	
	78%		Not Reported		100%	
	11		19		19	
Concurrent PI use	8		1		0	
Dosing interval (hours)	12	24	12	24	12	24
Administered dose (mg/kg)	4.04	8.02	4.05	8.1	4.7	9.6
AUC_{0-24} (mg*hr/L)	9.48[a]	8.66[a]	8.88[a]	9.80[a]	11.97[a]	12.99[a]
C_{max} (mg/L)	1.05[a]	1.87[a]	1.11[a]	2.09[a]	1.80[a]	3.17[a]
C_{min} (mg/L)	0.08[a]	0.05[a]	0.067[a]	0.056[a]	0.08[a]	0.05[a]
Cl/F/kg (L/hr/kg)	0.79[a]	0.86[a]	0.90[a]	0.80[a]	0.79[a]	0.72[a]

Data are medians except as noted.

[a] Geometric mean

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Lamivudine undergoes intracellular metabolism to its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unphosphorylated lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once- and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents aged 16 and older who weigh 50 kg or more.[27, 28]

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Stavudine (d4T, Zerit) (Last updated November 1, 2012; last reviewed November 1, 2012)

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, 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 (at least 14 days old and weighing <30 kg):

- 1 mg/kg twice daily

Adolescent (≥30 kg)/adult dose:

- 30 mg 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 [NRTIs]). The risk is increased when used in combination with ddI.
- 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other NRTIs:* Stavudine should not be administered in combination with zidovudine because of virologic antagonism.

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- *Overlapping toxicities:* The combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Reported toxicities are more often reported in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.
- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in HIV/hepatitis C virus co-infected patients receiving combination antiretroviral therapy (ART), interferon, and ribavirin.

Major Toxicities:

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral sensory neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a history of peripheral neuropathy, and in those patients receiving other drugs associated with neuropathy. Pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant women. This combination should not be used for initial therapy. Risk factors found to be associated with lactic acidosis in adults include female gender, obesity, and prolonged nucleoside exposure.[1]
- *Rare:* Increased liver enzymes and hepatic toxicity which may be severe or fatal. Neurologic symptoms including rapidly progressive ascending neuromuscular weakness are most often seen in the setting of lactic acidosis.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/d4T.html).

Pediatric Use: Although stavudine is FDA-approved for use in children, its use is limited because it carries a higher risk of side effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Data from multiple pediatric studies of stavudine alone or in combination with other antiretroviral agents demonstrate that stavudine appears safe and is associated with clinical and virologic response.[2-8] In resource-limited countries, stavudine is frequently a component of initial ART therapy with lamivudine and nevirapine in children, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte count and complete viral suppression in 50% to 80% of treatment-naive children.[9-12] In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving cotrimoxazole prophylaxis.[13]

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.[14, 15] In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest but significantly higher rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.[15] Peripheral neuropathy is an important

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toxicity associated with stavudine but appears to be less common in children than in adults.[3, 16] In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children.[15] Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.[17-20] Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy, with 9 children demonstrating lipoatrophy.[21] Among 90 children receiving stavudine, lamivudine, and either nevirapine or efavirenz, 65% developed lipodystrophy by 33 months.[22] Among 100 pre-pubertal African children, the prevalence of lipoatrophy was found to be 37% with a strong correlation with duration on stavudine therapy.[23] Improvements in lipodystrophy were observed among Thai children after substitution of stavudine with zidovudine.[24]

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine (ddI).[25-27] In adults, female gender, higher body mass index (BMI), and lower initial CD4 cell count are risk factors for developing lactic acidosis and hyperlactatemia.[1] The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available.[28] (For additional information on lactic acidosis see Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.)

Many of the above-mentioned adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues.[25, 29-31] In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.[32]

The World Health Organization recommends that stavudine be phased out of use because of unacceptable toxicity, with a strong recommendation that a maximum stavudine dose of 30 mg twice daily be used instead of the FDA-recommended 40 mg twice daily in patients weighing 60 kg or more.[33, 34] Several studies have compared the efficacy and toxicity of the two doses: HIV suppression was found to be similar in adults treated in South Africa with either the 30-mg or 40-mg dose;[35] in adults treated in South Africa, incidence of peripheral neuropathy was significantly lower in the 30-mg than in the 40-mg group, but the overall incidence was considered to be unacceptably high.[36] Lipoatrophy and peripheral neuropathy are more likely to occur with higher doses but the risk of lactic acidosis is associated with female gender and a high BMI.[33] Efficacy data are limited comparing the 30-mg and 40-mg doses given twice daily, but incidence of lipoatrophy and peripheral neuropathy are reduced when the lower doses are used.

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.[37] These early studies were conducted at a time when treatment options were limited and many children had failure to thrive. The authors in this early PK study state that stavudine distributes in total body water and because total body weight correlates well with lean body mass (or weight) stavudine dosages in obese children should be based on lean body weight.[37]

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, the appropriate dose drawn up into an oral syringe, and administered immediately. Because plasma exposure is equivalent with stavudine administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.[38]

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Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated November 1, 2012; last reviewed November 1, 2012)

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)

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

Combination tablets:

- *With emtricitabine (FTC):* 200 mg FTC + 300 mg TDF (Truvada)
- *With FTC + efavirenz (EFV):* 200 mg FTC + 600 mg EFV + 300 mg TDF (Atripla)
- *With FTC + rilpivirine (RPV):* 200 mg FTC + 25 mg RPV + 300 mg TDF (Complera)
- *With FTC + elvitegravir (EVG) + cobicistat (COBI):* 200 mg FTC + 150 mg EVG + 150 mg COBI + 300 mg TDF (Stribild)

Dosing Recommendations

Neonate/infant dose:
Not FDA approved or recommended for use in neonates/infants aged <2 years.

Pediatric dose (aged ≥2 years to <12 years)*:

- 8 mg/kg/dose once daily.

Oral powder dosing table

Body Weight Kilogram (kg)	Oral Powder Once Daily Scoops of Powder
10–<12	2
12–<14	2.5
14–<17	3
17–<19	3.5
19–<22	4
22–<24	4.5
24–<27	5
27–<29	5.5
29–<32	6
32–<34	6.5
34–<35	7
≥35	7.5

Selected Adverse Events

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

Special Instructions

- Oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix oral powder in 2–4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the oral powder with liquid: the powder may float on the top even after vigorous stirring.
- 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.
- Given the potential for TDF-induced changes in renal tubular function, some panel members recommend monitoring for proteinuria and glycosuria every 6–12 months.

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Tablets dosing table (aged ≥2 years and weight ≥17 kg)

Body Weight Kilogram (kg)	Tablets Once Daily
17–<22	150 mg
22–<28	200 mg
28–<35	250 mg
≥35	300 mg

Adolescent (aged ≥12 years and weight ≥35 kg)* and adult dose:

- 300 mg once daily

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

Combination Tablets

Truvada

- *Adolescent (aged ≥12 years and weight ≥35 kg) and adult dose:* 1 tablet once daily.

Atripla

- *Adolescent (aged ≥12 years and weight ≥40kg) and adult dose:* 1 tablet once daily.

Complera

- *Adult dose:* 1 tablet once daily in treatment-naive adults. Administer with a meal.

Stribild

- *Adult dose (aged ≥18 years):* 1 tablet once daily in treatment-naive adults. Administer with food

TDF in combination with didanosine (ddI):

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

TDF in combination with atazanavir (ATV):

- When ATV is used in combination with TDF, ATV should always be boosted with ritonavir (RTV).
- 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, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Metabolism

- Renal excretion.
- Dosing of TDF 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 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.

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Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (tenofovir).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with tenofovir and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors (PIs):* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir co-administered with tenofovir is atazanavir 300 mg with ritonavir 100 mg and tenofovir 300 mg, all as a single daily dose with food. Atazanavir without ritonavir should not be co-administered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.
- *Use with Stribild:* If using Stribild, please see the elvitegravir section of the drug appendix for additional information.

Major Toxicities:

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density (BMD) have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TDF.html).

Pediatric Use: Tenofovir is Food and Drug Administration (FDA) approved for use in children aged ≥2 years when used as a component of the two-NRTI backbone in combination antiretroviral therapy (cART).

The standard adult dose of tenofovir approved by the FDA for adults and children aged ≥12 years and weight ≥35 kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 mg/m^2/dose used in early studies in children.[1]

In adults, the recommended dose is highly effective.[2, 3]

In children aged 12 to <18 years, no difference in viral load response was seen between 2 treatment groups in a randomized, placebo-controlled trial of tenofovir 300 mg once daily or placebo, plus an optimized background regimen, in 87 treatment-experienced adolescents in Brazil and Panama.[4-6] Subgroup analyses suggest this lack of response was from imbalances in viral susceptibility to the optimized background regimens.

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In children aged 2 to <12 years, tenofovir 8 mg/kg/ dose once daily showed non-inferiority to zidovudine- or stavurdine-containing cART over 48 weeks of randomized treatment using a snapshot analysis (product label). This was a switch study in children aged 2 to 12 years with viral load <400 copies/mL during treatment with zidovudine or stavudine as part of cART, randomized to continue their zidovudine or stavudine (N=49) or switch to tenofovir (N=48) while continuing other components of the regimen (Gilead study 352).[4]

Other pediatric studies have also shown that virologic success is related to prior treatment experience. In 115 pediatric patients treated with tenofovir, viral load decreased to <50 copies/mL at 12 months in 50% of patients on first-line therapy, 39% of patients on second-line therapy, and 13% of patients on third-line or subsequent therapy.[7] This cohort used a target dose of 8 mg/kg, but 18% of patients were dosed at greater than 120% of the target dose and 37% were dosed at less than 80% of the target dose.

Virologic success is also related to drug exposure. In a study using a median daily dose of 208 mg/m^2, [8] lower single-dose and steady-state area under the curve (AUC) were associated with inferior virologic outcome.

Pharmacokinetic (PK) studies in children receiving an investigational 75-mg tablet formulation of tenofovir showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and maximum plasma concentration (C_{max}) that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg.[1, 9] Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure.[1] This lower exposure occurred even though participants were concurrently treated with ritonavir, which boosts tenofovir exposure. Lower-than-anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir.[10]

Further studies are needed of tenofovir PK and clinical outcomes in children, especially when used in combinations that do not include lopinavir and/or ritonavir.

Decreases in BMD have been reported in both adult and pediatric studies. Younger children (Tanner Stages 1 and 2) may be at higher risk than children with more advanced development (Tanner Stage ≥3).[1, 11, 12] In a Phase I/II study of an investigational 75-mg formulation of tenofovir in 18 heavily pretreated children and adolescents, a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DXA) scan was reported in 5 of 15 (33%) children evaluated at Week 48.[1] Two of the 5 children who discontinued tenofovir at 48 weeks experienced partial or complete recovery of BMD by 96 weeks.[13] Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years.[8, 13] In a second study of 6 patients who received the commercially available, 300 mg formulation of tenofovir, 2 pre-pubertal children experienced >6% BMD decreases. One of the 2 children experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her cART regimen with subsequent recovery of BMD.[14] Loss of BMD at 48 weeks was associated with higher drug exposure.[8]

In the industry-sponsored study that led to FDA approval of tenofovir in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm[4, 5] (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM209151.pdf).

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In the Gilead switch study (352) in children aged 2 to 12 years over the 48 weeks of randomized treatment, total body BMD gain was less in the tenofovir group than in the zidovudine or stavudine group, but the mean rate of lumbar spine BMD gain was similar between groups. At 48 weeks all participants were offered tenofovir, and for the participants who were treated with the drug for 96 weeks, total body BMD *z* score declined by -0.338 and lumbar spine BMD *z* score declined by -0.012.[4]

Not all studies of tenofovir in children have identified a decline in BMD.[15, 16] No effect of tenofovir on BMD was found in a study in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz.[17] All patients in this study remained clinically stable and virologically suppressed after switching to the new regimen.[18]

New onset or worsening of renal impairment has been reported in adults and children receiving tenofovir and may be more common in those with higher tenofovir trough plasma concentrations.[19] Possible tenofovir -associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance (CrCl), and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including lopinavir/ritonavir and didanosine for 1 year.[20] Irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine.[21] Renal toxicity leading to discontinuation of tenofovir was reported in 3.7% (6 of 159) of HIV-1-infected children treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland.[7] Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 27% (12 of 44) of children treated with tenofovir compared with 4% (2 of 48) of children not treated with tenofovir.[22] An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing cART.[23] Prospectively evaluated renal function was reported for a cohort of 40 pediatric patients on tenofovior-containing antiretroviral regimens from 5 Spanish hospitals. The patients ranged in age from 8 to 17 years (median age 12.5 years) and had received tenofovir for 16 to 143 months (median 77 months). The following observations were made: 18 patients had declines in CrCl after at least 6 months of therapy; 28 patients had decreases in tubular reabsorption of phosphate, which worsened with longer time on tenofovir; and 33 patients had proteinuria, including 10 patients with proteinuria in the nephrotic range.[24] However, no significant decrease in calculated glomerular filtration rate was found in 26 HIV-infected children treated with tenofovir for 5 years.[25] Of 89 participants who received tenofovir in Gilead study 352 (median drug exposure 104 weeks), 4 discontinued from the study for renal tubular dysfunction, and 3 of whom had hypophosphatemia and decrease in total body or spine BMD *z* score.[4]

Given the potential for BMD loss in children treated with tenofovir, some experts recommend obtaining a DXA before initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner Stages 1 and 2). Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in early adolescence is concerning and favors judicious use of tenofovir in this age group.

The taste-masked granules that make up the oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed in the vehicle, if allowed to sit too long, the taste becomes bitter.

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Zidovudine (ZDV, AZT, Retrovir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Combination tablets:

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

Dosing Recommendations

ZDV dose for neonates/infants (<6 weeks of age) for prevention of transmission or treatment (Note: standard neonate dose may be excessive in premature infants)**:**

Gestational Age (weeks)	ZDV Oral Dosing	ZDV Intravenous Dosing (if unable to tolerate oral agents)
≥35 weeks	4 mg/kg of body weight every 12 hours	3 mg/kg of body weight IV every 12 hours
≥30–<35 weeks	2 mg/kg of body weight every 12 hours during first 14 days of life; increased to 3 mg/kg every 12 hours aged ≥15 days	1.5 mg/kg of body weight IV every 12 hours during first 14 days of life; increased to 2.3 mg/kg every 12 hours aged ≥15 days
<30 weeks	2 mg/kg of body weight every 12 hours during first 4 weeks of life; increased to 3 mg/kg every 12 hours after age 4 weeks	1.5 mg/kg of body weight IV every 12 hours until 4 weeks of life; increased to 2.3 mg/kg every 12 hours after age 4 weeks

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.

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

- *Body surface area dosing:*
  Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours.

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 (age ≥18 years)/adult dose:

- 300 mg twice daily.

Combivir

Adolescent (weight ≥30 kg)/adult dose:

- 1 tablet twice daily.

Trizivir

Adolescent (weight ≥40 kg)/adult dose:

- 1 tablet twice daily.

Metabolism

- Metabolized to AZT glucuronide, which is renally excreted.
- 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 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.

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine should not be administered in combination with stavudine because of virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Incidence of neutropenia may be increased in infants receiving lamivudine.[1]
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.[2]

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Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ZDV.html).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy.[3]

Pediatric Use: Zidovudine is frequently included as a component of the NRTI backbone for antiretroviral therapy.[4-20] Pediatric experience with zidovudine both for treatment of HIV and for prevention of mother-to-child transmission (PMTCT) is extensive.

Perinatal trial PACTG 076 established that zidovudine prophylaxis given during pregnancy, labor, and delivery, and to the newborn reduced risk of perinatal transmission of HIV by nearly 70%[21] (see the 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 further discussion on the use of zidovudine for PMTCT of HIV). Although the PACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice daily oral infant dosing for prophylaxis. Zidovudine 4 mg/kg of body weight every 12 hours is now recommended for neonates/infants >35 weeks of gestation for prevention of transmission or treatment (see *Perinatal Guidelines*).

Overall, zidovudine pharmacokinetics (PKs) in pediatric patients aged >3 months are similar to those in adults. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing is not recommended because of low intracellular zidovudine triphosphate concentrations seen with 600-mg once-daily dosing in adolescents.[22] PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age.[5] Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease.[23]

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Appendix A: Pediatric Antiretroviral Drug Information

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

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Efavirenz (EFV, Sustiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Combination Tablets:

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

Dosing Recommendations

Neonate/infant dose:

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

Pediatric dose:

- *Children aged <3 years:*
  No data are currently available on the appropriate EFV dosage for children aged <3 years.
- *Children aged ≥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/m^2 of body surface area (maximum dose 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.

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
- 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

- 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 female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).

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Atripla

- Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.
- *Adult dose:* One tablet once daily
- CYP3A4 and CYP2B6 substrate.
- Dosing of EFV 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, 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 text for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions. Importantly, dosage adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities, such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.
- *Rare:* Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as Food and Drug Administration (FDA) Pregnancy Class D, which means that there is positive evidence of human fetal risk based on studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester (the primary period of fetal organogenesis) whenever possible. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and should be counseled about the potential risk to the fetus and desirability of

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avoiding pregnancy. Alternate antiretroviral (ARV) regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (if such alternative regimens are acceptable to provider and patient and will not compromise the woman's health).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/EFV.html).

Pediatric Use: Efavirenz is FDA-approved for use as part of antiretroviral therapy in children aged 3 years or older who weigh at least 10 kg. Limited pharmacokinetic (PK) data in children younger than age 3 or who weigh less than 13 kg have shown that it is difficult to achieve target trough concentrations in this age group, even with very high (>30 mg/kg) doses of an investigational liquid formulation.[1] Thus, efavirenz is not recommended for use in children younger than age 3 years at this time, and no liquid formulation is commercially available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children. P1070 is an ongoing study collecting data on efavirenz dosing in HIV-infected and HIV/tuberculosis-co-infected children younger than age 3 years. In addition, efavirenz should be used with caution in adolescent women of childbearing age because of the potential risk of teratogenicity.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 is the primary enyzme for efavirenz metabolism, and pediatric patients with the 516 T/T or G/T genotype have reduced metabolism and higher efavirenz levels compared with those with the G/G genotype.[2, 3] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults.[4, 5]

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1 mcg/mL in adults.[6] Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA levels less than or equal to 400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL).[7] In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration (C_{min}) levels greater than 1.1 mcg/mL or area under the curve (AUC) greater than 51 mcg*h/mL.[8] Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal.[2, 8-11] Therefore, some experts recommend therapeutic drug monitoring with efavirenz and possibly use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered efavirenz dose was 13 mg/kg (367 mg/m^2) and the range was from 3 to 23 mg/kg (69–559 mg/m^2).[7] A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m^2 twice daily plus efavirenz 350 mg/m^2 once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.[12] Therapeutic drug monitoring can be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported in up to 40% of children compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset

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is typically during the first 2 weeks of treatment.[13] Although severe rash and Stevens-Johnson syndrome (SJS) have been reported, they are rare. In adults, CNS symptoms have been reported in more than 50% of patients.[14] These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. Ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric adverse effects. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations.[6, 15-18] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies[13] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.[3] CNS adverse effects may be harder to detect in children because of the difficulty in assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

Therapeutic drug monitoring (TDM) can be considered for children with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In that situation, it is reasonable for a clinician to use therapeutic drug monitoring to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.[19, 20] This is the only setting in which dose reduction would be considered appropriate management of drug toxicity and, even then, it should be used with caution.

Efavirenz should not be used by women who desire to become pregnant or who do not use effective, consistent contraception. Efavirenz should not be used throughout the first trimester of pregnancy because of the potential risk of teratogenicity[21] (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*[22]). Alternative ARV regimens that do not include efavirenz should be strongly considered for use in sexually active adolescent females because of the potential for inconsistent use of contraception and the high risk of unintended pregnancy.

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Etravirine (ETR, Intelence, TMC 125) (Last updated November 15, 2012; last reviewed November 1, 2012)

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 at least 16 kg):

Weight in kilograms (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.

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. The type of food does not affect the exposure to ETR.
- ETR tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medication, stir well until the water looks milky; if desired, add more water or alternatively orange juice or milk (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 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

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patients with renal impairment.

Metabolism

- ETR is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (Pgp). It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple drug interactions (see below).

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- Etravirine is associated with multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions with ETR.
- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors. It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, efavirenz, or rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,[1] but no dose adjustment is currently recommended when etravirine and raltegravir are used together.

Major Toxicities:

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common (more severe):* Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (HSRs) (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ETR.html).

Pediatric Use: Etravirine is FDA-approved for use in antiretroviral-experienced children and adolescents aged 6 to 18 years.

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A Phase I dose-finding study involving children aged 6–17 years, with virologic suppression on a stable lopinavir/ritonavir-containing regimen compared doses of 4 mg/kg twice daily and 5.2 mg/kg twice daily using both the investigational 25-mg tablets and the available 100-mg formulation.[2] Etravirine therapy was added for 8 days and pharmacokinetic (PK) sampling and analysis were performed. Among 17 children given 4 mg/kg twice daily, the PK parameters AUC_{12h} and C_{min} were below preset statistical targets compared with these parameters in adults. By comparison, acceptable PK were observed for participants who received 5.2 mg/kg twice daily, including 12 patients aged 6 to <12 years, and 9 study participants ages 12 to 17 years. The higher dose (5.2 mg/kg twice daily; [maximum 200 mg per dose]) was chosen for evaluation in the PIANO study (TMC125-C213), a single-arm, Phase II trial evaluating the PK, safety, tolerability, and efficacy of etravirine in 101 ARV treatment-experienced HIV-1 infected pediatric subjects aged 6 to <18 years and weighing ≥16 kg.[3] Subjects eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA of at least 500 copies/mL and viral susceptibility to etravirine at screening. The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/mL, and the median baseline CD4 T lymphocyte (CD4 cell) count was 385 x 10^6 cells per mm^3. At Week 24, 67% of these pediatric subjects had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. The mean CD4 cell count increase from baseline was 112 x 10^6 cells per mm^3. The population PK data from this Phase II trial (101 treatment-experienced children aged 6–17 years) revealed slightly lower etravirine exposures in adolescents (aged 12–17 years) compared with children aged 6 to 11 years and with adults (see table below).

	Mean AUC_{12} (ng*h/mL)	**Mean C_{0h} (ng/mL)**
Children aged 6–11 years (N=41)	5764	381
Adolescents aged 12–17 years (N=60)	4834	323
All Pediatric Participants	5236	347
Adults	5506	393
AUC_{12} = Area under the curve for 12h post dose; C_{0h} = pre-dose concentration during chronic administration.		

The frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adult subjects, except for rash, which was observed more frequently in pediatric subjects. The most common adverse drug reactions (in at least 2% of pediatric subjects) were rash and diarrhea. Rash (≥Grade 2) occurred in 15% of pediatric subjects. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared with male subjects.

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluted in a multicenter retrospective study of 23 multidrug-resistant pediatric patients with a median age of 14.2 years (interquartile range 12.5 to 15.8 years).[4] The median baseline HIV-1 RNA was 4.5 $\log_{10}$ HIV-1 RNA copies/mL and the median CD4 T-cell count was 445 cells/mm^3. The backbone regimen included at least two fully active drugs in 91% of patients. During a median of 48.4 weeks of follow-up, 20 patients (87%) achieved HIV-1 RNA<400 copies/mL and 18 of 23 (78%) achieved HIV-1 RNA<50 copies/mL. No patients showed complete resistance to etravirine after follow up but 3 of the 21 patients who interrupted etravirine treatment because of virological or immunological failure had single resistance mutations at baseline.

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The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multi-center retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit et al found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4.[5]

Etravirine is often combined with ritonavir-boosted darunavir for treatment of HIV-infected adults with prior virologic failure. King et al[6] examined PK data from 37 pediatric patients receiving this combination, all receiving the maximum 200 mg etravirine dose. For both drugs, the estimated 90% confidence intervals for AUC and C_{min} fell below targeted lower limits defined using data from studies in adults. While this combination has been effective in a small cohort of HIV-infected adolescents,[7] these data suggest a need for continued study of PK interactions involving etravirine and other ARV agents in pediatric patients.

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Nevirapine (NVP, Viramune) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 (aged <14 days):

- When used for prevention of mother-to-child transmission of HIV see *Perinatal Guidelines*. Treatment dose not defined for infants aged ≤14 days.

Pediatric dose (aged ≥15 days):

See note below about initiation of therapy.

Aged <8 years:

- 200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

Aged ≥8 years:

- 120–150 mg/m^2 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 age 8 years; rather, the mg dose is left static to achieve the appropriate mg/m^2 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 P45-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 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

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

- 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 dose until rash resolves (see *Major Toxicities*).
- NVP XR tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see text below).
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests 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 liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.

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Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

- 400 mg XR 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 NVP 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.

- Shake suspension well and store at room temperature

Metabolism

- Metabolized by cytochrome P450 (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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Metabolism:* Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; auto-induction of metabolism occurs in 2 to 4 weeks, with a 1.5- to 2-fold increase in clearance. Potential exists for multiple drug interactions. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than efavirenz. Altered adverse effect profiles related to elevated nevirapine levels have not been documented, probably because there are alternative CYP metabolic pathways for nevirapine.[1] Please see efavirenz section for further details.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be co-administered to patients receiving atazanavir (with or without ritonavir).

Major Toxicities:

Note: These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated hepatic transaminases. 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. However, the risk of

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developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against a patient's overall ability to tolerate the regimen and the current antiviral response.

- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). Most cases occur in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 T lymphocyte (CD4 cell) count at time of therapy initiation (CD4 cell count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). In children, recent results indicate that there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.[2] Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NVP.html).

Pediatric Use: Nevirapine is U.S. Food and Drug Administration (FDA) approved for use in children from infancy onwards and remains a mainstay of therapy, especially in resource-limited settings. It has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI).[3-11]

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission, nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-based ART to control virus load. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as <1 log decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24), compared with 7% in the zidovudine/lamivudine/lopinavir/ritonavir arm, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, $P = 0.027$.[12] A comparison study of nevirapine versus lopinavir/ritonavir in children aged 6 to 36 months not previously exposed to nevirapine has reported similar results, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[13]

Body surface area has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid under dosing of nevirapine because a single point mutation in the HIV genome may confer non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children (aged ≤8 years) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.[8, 9] Because of this, it is recommended that dosing for children aged <8 years be 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children aged 8 years, the recommended dose is 120 mg/m^2 of

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body surface area per dose (maximum dose 200 mg) administered twice daily. When adjusting the dose in a growing child, the milligram dosage need not be decreased (from 200 mg/m^2 to 120 mg/m^2) as the child reaches 8 years; rather, the milligram dose is left static as long as there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m^2 dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

The potential for under dosing with an increased risk of resistance has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of nevirapine is initiated with a single daily dose during the first 2 weeks of treatment to allow for auto-induction of the liver enzymes CYP3A and CYP2B6 (which are involved in nevirapine metabolism). Studies, largely in adult cohorts, indicated the potential for greater drug toxicity without this half-dose lead-in.[14] The CHAPAS-1 Trial[15] randomized 211 children to initiate ART with either half dose or full-dose nevirapine. Children were followed for a median of 92 weeks (68–116 weeks), and there was no difference in grade 3 or 4 adverse events between the 2 groups. The full-dose nevirapine group had a statistically significant increase in grade 2 rash, but most subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. Additional trials are either in development or are under way to further evaluate the potential of initiating nevirapine therapy at full dose in treatment-naive children. Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,[16] and the results of CHAPAS-1, the Panel recommends restarting nevirapine at full dose in children who interrupt therapy for 14 days or less.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients on the basis of 2 trials: VERxVE and TRANxITION. VERxVE[17] enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. VERxVE and TRANxITION have shown equivalent efficacy, adverse effect, and CD4 profiles through 48 and 24 weeks, respectively.[18] Trials are under way on use of extended-release nevirapine in patients aged <18 years.

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Rilpivirine (RPV, Edurant, TMC 278) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Tablet: 25 mg

Combination Tablet:
- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  RPV 25 mg + FTC 200 mg + TDF 300 mg (Complera)

Dosing Recommendations

Neonate/infant dose:
- Not approved for use in neonates/infants.

Pediatric dose:
- Not approved for use in children. A clinical trial in treatment-naive adolescents (aged 12–18 years) is under way.

Adolescent (>18 years of age)/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 of at least 500 calories (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.
- Use rilpivirine with caution when co-administered 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 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.

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Drug Interactions:

- *Metabolism:* Rilpivirine is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before rilpivirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

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

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html).

Pediatric Use: The pharmacokinetics, safety, and efficacy of rilpivirine in pediatric patients have not been established. An international trial currently under way is investigating a 25-mg dose of rilpivirine in combination with two nucleoside reverse transcriptase inhibitors in antiretroviral-naive children aged 12 to 18 years who weigh at least 40 kg.

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Appendix A: Pediatric Antiretroviral Drug Information

Protease Inhibitors

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Fosamprenavir (FPV, Lexiva)

Indinavir (IDV, Crixivan)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Nelfinavir (NFV, Viracept)

Ritonavir (RTV, Norvir)

Saquinavir (SQV, Invirase)

Tipranavir (TPV, Aptivus)

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Atazanavir (ATV, Reyataz) (Last updated November 1, 2012; last reviewed November 1, 2012)

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:

- 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 in children aged <6 years.

For children aged ≥6 to <18 years:

Weight (kg)	Once-Daily Dose
15–<20 kg	ATV 150 mg + RTV 100 mg, both once daily with food
20–<32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32–<40 kg	ATV 250 mg* + RTV 100 mg, both once daily with food
≥40 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Dose in mg requires two different capsule strengths of ATV. Additional patient education should be considered to avoid dosing errors (see text for discussion).

- *For treatment-naive pediatric patients who do not tolerate ritonavir (RTV):* **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.** Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children aged <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*).
- Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

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.
- Additional patient education should be considered to avoid dosing errors when prescribing ATV 250 mg because this dose requires 2 different capsule strengths of ATV.
- 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 co-administered with H2 receptor antagonists). When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.

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Adolescent (aged ≥18–21 years)/adult dose:
Antiretroviral-naive 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-naive 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.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is co-administered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive 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. Co-administration of ATV 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.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucoronosyltransferase (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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Atazanavir is both a substrate and an inhibitor of the cytochrome P (CYP) 3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- A patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug is administered.

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- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be co-administered with atazanavir in treatment-experienced patients but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naive adults.
- *Integrase Inhibitors:* Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.
- *Absorption:* Atazanavir absorption is dependent on low gastric pH. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors (PPIs) in adults are as follows:

- *Antacids:* Atazanavir concentrations are decreased when the drug is co-administered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted atazanavir in treatment-naive patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the antiretroviral (ARV) agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2 receptor antagonist (a single dose of an H2 receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-Receptor Antagonists (boosted atazanavir in treatment-naive or -experienced patients):* H2 receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H2 receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily for treatment-naive patients or a ≤20-mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (ATV 300 mg + RTV 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist.
- *H2-Receptor Antagonists (boosted atazanavir with tenofovir):* Treatment-experienced patients using both tenofovir and H2-receptor antagonists should be given an increased dose of atazanavir (ATV 400 mg + RTV 100 mg + TDF 300 mg).
- *PPIs:* Coadministration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naive patients are ≤20-mg dose equivalent of omeprazole taken approximately 12 hours before boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with PPIs is not recommended in treatment experienced patients.

Major Toxicities:

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus, but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.
- *Less common:* Prolongation of PR interval of electrocardiogram. Abnormalities in atrioventricular (AV) conduction generally limited to first-degree AV block, but with rare reports of second-degree

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AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other protease inhibitors (PIs). However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or hepatitis C are at increased risk).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ATV.html).

Pediatric Use: Atazanavir is FDA-approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children aged ≥6 years.

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic (PK) targets, but only when used at higher doses of atazanavir (on a mg/kg body weight or mg/m^2 body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children older than 6 and younger than 13 years of age required atazanavir dosing of 520 mg/m^2 of body surface area per day of atazanavir capsule formulation to achieve PK targets. Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents aged >13 years required atazanavir dosing of 620 mg/m^2 of body surface area per day.[1] In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir groups but the maximum plasma concentration (C_{max}) was higher and minimum plasma concentration (C_{min}) lower for the unboosted arms. Median doses of atazanavir in mg/m^2 both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.[2] Higher target trough concentrations may be required in protease inhibitor (PI)-experienced patients.

Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[1]

Age range (years)	Was ATV given with RTV boosting?	ATV median dose (mg/m^2*)	ATV median dose (mg*)
6–13 years	No	509	475
6–13 years	Yes	208	200
>13 years	No	620	900
>13 years	Yes	195	350

* Dose satisfied protocol-defined AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM was used to determine patient-specific dosing in this trial.

Regarding toxicity, 8.5% (11 of 129) of patients enrolled in the trial had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (ECG) abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 patients. No significant changes in serum cholesterol or triglycerides

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were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs.[3, 4]

A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following atazanavir/ritonavir doses: 150/100 mg (15–<20 kg), 200/100 mg (20–<40 kg), 300/100 mg (≥40 kg)[5] and the current FDA-approved product label recommends these weight-based doses. The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[5] The authors acknowledge that atazanavir/ritonavir at 250/100 mg appeared to be a more appropriate dose than atazanavir/ritonavir at 200/100 mg for the 35 to <40 kg weight group; however, this dose was not recommended in the product label because the 250 atazanavir dosage strength requires the use of 2 different capsule strengths and is prone to dosing errors.[5]

The doses of atazanavir/ritonavir recommended by the Pediatric ARV Guideline Panel are 200/100 mg for pediatric patients weighing 20 to <32 kg and 250/100 mg for patients weighing 32 to <40 kg while the FDA-approved dose of atazanavir/ritonavir is 200/100 mg for pediatric patients weighing 20 to <40 kg. The higher dose of 250/100 mg is recommended by the Pediatric ARV Guideline Panel at the 32 to <40 kg weight band to avoid underdosing. Additional patient education to prevent dosing errors is recommended when 250 mg of atazanavir is prescribed because this dosage requires the use of 2 different capsule strengths of atazanavir.

A population PK study of 51 children with mean age 14.3 years and weight 51 kg that targeted mean adult exposure for a 300/100 mg atazanavir/ritonavir dosage showed that the following atazanavir/ritonavir doses might be an appropriate alternative to the FDA recommendations: 200/100 (25–39 kg), 250/100 mg (39–50 kg) and 300/100 (>50 kg).[6] In addition, simulations suggested that the following doses should be used in children when combined with 300 mg tenofovir disoproxil fumarate (TDF): 250/100 mg for children weighing 35 to 39 kg, then 300/100 mg for children weighing over 39 kg.[6] The authors conclude that these recommendations should be prospectively confirmed.[6]

In a small, single-site study, 23 pediatric patients (median age 16 years) on combination antiretroviral therapy were switched to a once-daily ritonavir-boosted atazanavir-containing regimen because of virologic failure (12 patients) or for treatment simplification (11 patients).[7] Twenty of the patients had previously received PI-based regimens with the median number of two atazanavir-associated mutations acquired before switching to atazanavir/ritonavir. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine. Both tenofovir and buffered didanosine have known drug interactions with atazanavir and can lower plasma concentrations. In this study, atazanavir plasma concentrations were measured at 12 to 15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients who previously had undetectable viral loads experienced virologic failure; 6 of 12 patients who previously had virologic failure achieved undetectable viral loads.

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Darunavir (DRV, Prezista) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Oral suspension: 100 mg/mL

Dosing Recommendations

- DRV should not be used without ritonavir (RTV).

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- *Age <3 years:*

Do not use DRV in children younger than age 3 years because of concerns related to seizures and death in infant rats associated with immaturity of the blood-brain barrier and liver metabolic pathways.

- *3 to <18 years of age and weighing ≥10 kg:*

Weight	Dose (both twice daily[a] with food)
10–<11 kg	DRV 200 mg (2 mL) + RTV 32 mg (0.4 ml[b])
11–<12 kg	DRV 220 mg (2.2 mL) + RTV 32 mg (0.4 ml[b])
12–<13 kg	DRV 240 mg (2.4 mL) + RTV 40 mg (0.5 ml[b])
13–<14 kg	DRV 260 mg (2.6 mL) + RTV 40 mg (0.5 ml[b])
14–<15 kg	DRV 280 mg (2.8 mL) + RTV 48 mg (0.6 ml[b])
15–<30 kg	DRV 375 mg (tablets or 3.75 mL oral suspension) + RTV 50 mg (0.6 ml[b])[c]
30–<40 kg	DRV 450 mg + RTV 60 mg (0.8 ml[b])[c]
≥40 kg	DRV 600 mg + RTV 100 mg

[a] *Do not use once-daily dosing in children aged <12 years or in any patient aged <18 years who is treatment-experienced (prior treatment failure). Once-daily dosing*

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

- DRV 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.
- DRV contains a sulfonamide 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. Careful instruction to caregivers is important. Pill burden may have a negative effect on adherence.
- Store DRV tablets and oral suspension at room temperature (25ºC or 77ºF). Oral suspension should be stored in the original container and shaken well before dosing.
- **Do not use once daily for:** children aged <12 years; for youth ages 12–18 years if treatment experienced (prior treatment failure); or in

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(DRV 800 mg + RTV 100 mg can be used in treatment-naive pediatric patients aged 12–18 years and weighing ≥40 kg but is not FDA-approved for this population (see text). Note that the dose in children weighing 10–15 kg is 20 mg/kg body weight per dose, higher than the weight-adjusted dose in heavier (older) children.

[b] *RTV supplied as 80mg/mL oral solution.*

[c] *To enhance palatability—RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation for children ≥20 kg, even though the RTV dose is higher.*

Adolescent (aged ≥18 years)/adult dose (treatment-naive or antiretroviral-experienced with no DRV resistance associated mutations):

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

Adolescent (aged ≥18 years)/adult dose (treatment experienced with at least one DRV resistance-associated mutation):

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

those aged ≥18 years if any of these DRV resistance associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- Dosing in patients with hepatic impairment: DRV 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 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). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. Potential exists for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome. Fever and elevated hepatic transaminases. Lipid abnormalities.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (such as hepatitis B or hepatitis C virus co-infection, or those with baseline elevation in transaminases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/DRV.html).

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Pediatric Use: Darunavir boosted with ritonavir is Food and Drug Administration (FDA) approved for use twice daily in combination with ritonavir in children aged 3 years and older as part of combination antiretroviral therapy (cART), but is not FDA-approved for once-daily use in those younger than age 18 years.

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric participants ages 6 to <18 years and weighing ≥20 kg. The participants had a median age of 14 years (range 6–<18 years) and 71% were male, 54% were white, 30% black, 9% Hispanic, and 8% other race/ethnicity. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least two non-protease inhibitor antiretroviral (ARV) drugs.[1] The study was a two-part Phase II trial to evaluate the pharmacokinetics and tolerance of darunavir/ritonavir in children. In Part I, a weight-adjusted dose of darunavir 9 to 15 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with 24-hour area under the curve (AUC_{24h}) of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult pharmacokinetic parameters. A pediatric dose 20% to 33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 to 19 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily. This resulted in darunavir AUC_{24h} of 123,276ng*h/mL (range 71,850–201,520) and C_{0h} of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation, all patients were allowed to switch to ritonavir 100-mg capsules, if desired, to avoid use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight-band doses of darunavir/ritonavir were chosen as follows: 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. As reported in the FDA clinical review (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129560.pdf), for the 80 participants the Week 24 viral load was <400 copies/mL and <50 copies/mL in 66% and 51% respectively[2] (FDA snapshot analysis), and only 1 participant withdrew for an adverse event.

In this study, 27 of the 80 participants[1] switched from the ritonavir liquid solution to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. A separate study in 19 Thai children[3] used ritonavir 100 mg twice daily as the boosting ritonavir dose, with darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30 to 40 kg), and 600 mg twice daily (body weight ≥40 kg). The darunavir exposures of twice-daily darunavir doses boosted with 100 mg ritonavir twice daily showed values similar to those obtained with lower ritonavir doses. This regimen was well tolerated and adds further support to boosting with the easier to tolerate 100-mg capsule of ritonavir twice daily even in children as young as aged 6 years or weighing as little as 20 kg. Data are not available to evaluate the safety and tolerability of using ritonavir 100 mg in children who weigh less than 20 kg.

Darunavir oral suspension administered twice daily with ritonavir boosting has been studied in children aged 3 to <6 years and weighing 10 to <20 kg, reported in,[4] and in an FDA Clinical review.[2, 5] This trial was in N = 27 children ages 3 to <6 years who were failing their current antiretroviral therapy regimens and had fewer than 3 darunavir resistance-associated mutations on genotype testing. Participants were enrolled from Argentina, Brazil, India, Kenya, and South Africa. The initial dose for study was darunavir 20 mg/kg with ritonavir 3 mg/kg, both given twice daily, but higher-than-anticipated doses were required to achieve target drug exposures. Therefore, the dose used in these studies in this age and weight group

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was increased to darunavir 25 mg/kg body weight combined with ritonavir 3 mg/kg body weight for children between 10 and 15 kg, and darunavir 375 mg plus ritonavir 50 mg for children 15 to <20 kg body weight. After dose adjustment, the darunavir AUC (0–12h), measured as a percent of the adult value, was 128% overall, 140% in the 10 to <15 kg weight band, and 122% in participants who weighed 15 to <20 kg (page 44 in http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf). At study week 24, 16 of 27 (59%) of these treatment-experienced subjects aged 3 to 6 years had viral load <50 copies/mL. This compares to a 75% virologic success rate in the 6- to 12-year-olds, and 39% in subjects aged 12 to 18 years (virologic success defined as viral load <50 copies/mL at 24 weeks) (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287673.pdf). Diarrhea, vomiting, and rash were the most common side effects. The taste of the darunavir liquid is said to be better than the poor taste of the ritonavir needed for PK boosting, which is seen as a greater challenge to palatability.

When the study was completed, re-analysis of the PK data suggested that a dose of darunavir 20 mg/kg plus RTV 3 mg/kg body weight would be acceptable (table), and that re-analysis led to the final dosing recommendations found in the FDA product label.

Table. Darunavir Pharmacokinetic Results from Multiple Studies

Population	N	Dose of DRV/RTV and frequency	AUC_{24h}[a] (mcg*h/mL) median[b]	C_{0h} (ng/mL) median[b]
10–<15 kg[c]	13	20/3 mg/kg twice daily	122.0	3,533
10–<15 kg[c]	4	25/3 mg/kg twice daily	238.0	8,522
15–<20 kg[c]	11	20/3 mg/kg twice daily	108.4	3,387
15–<20 kg[c]	14	25/3 mg/kg twice daily	137.2	4,365
Aged 6–<12 years[d]	24	Weight bands,[d] twice daily	112.8	3,354
Aged 12–<18 years[d]	50	Weight bands,[d] twice daily	132.8	4,059
Adults aged >18 years (3 studies)[e]	285, 278, 119	600/100 mg twice daily	109.4–123.3	3,197–3,539
Once Daily				
Ages 12–17 (mean 14.6)[8]	12	800/100 once daily	87.9	2,196
Adults aged >18 years (2 studies)[e]	335, 280	800/100 once daily	87.8-87.9	1,896- 2,041

[a] For twice-daily (BID) dosing, AUC_{24h} is calculated as 2 times the AUC_{12h}.

[b] When more than two studies are included, a range of medians is listed.

[c] FDA pharmacokinetics review 2011 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf)

[d] Weight band dosing was with darunavir/ritonavir at doses of 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. Data from FDA pharmacokinetics review 2008 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=darunavir&utm_content=10)

[e] Product label

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When darunavir plus ritonavir twice daily was used in combination with etravirine in 40 HIV-infected patients aged 11 to 20 years, both darunavir and etravirine exposure were lower than that found in adults.[6] When darunavir plus ritonavir twice daily was used in combination with tenofovir in 13 HIV-infected patients aged 13 to 16 years, both tenofovir and darunavir exposures were lower than those found in adults treated with the same combination.[7]

Although darunavir is approved for once-daily dosing in ARV-naive adults, it should not be used once daily in children less than age 12 years because of more rapid clearance and absence of pediatric data. One small study (N = 12) of once-daily dosing (DRV 800 mg + RTV 100 mg) in treatment-naive adolescents aged 12 to 17 years and weighing ≥40 kg demonstrated good Week 24 virologic responses and darunavir exposures similar to those seen in adults treated with once-daily darunavir (see table above).[8]

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Fosamprenavir (FPV, Lexiva) (Last updated November 1, 2012; last reviewed November 1, 2012)

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–18 years):

- Unboosted FPV (without ritonavir [RTV]) is FDA-approved for antiretroviral (ARV)-naive children aged 2–5 years, but not recommended by the Panel because of low exposures (see text below).
- Boosted FPV (with RTV) is FDA-approved for ARV-naive infants at least 4 weeks of age and for treatment experienced infants at least 6 months of age; 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.

Aged ≥6 months–18 years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients at Least 6 Months of Age Using Lexiva Oral Suspension With Ritonavir

Weight	Dose FPV + RTV Both twice daily* with food
<11 kg	FPV 45 mg/kg + RTV 7 mg/kg
11 kg–<15 kg	FPV 30 mg/kg + RTV 3 mg/kg
15 kg–<20 kg	FPV 23 mg/kg + RTV 3 mg/kg
≥20 kg	FPV 18 mg/kg + RTV 3 mg/kg

*Not to exceed the adult dose of FPV 700 mg + RTV 100 mg twice daily.

Note: When administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (FPV 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

- 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 oral suspension well before 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 it is absorbed.

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twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

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

Adolescent (aged >18 years)/adult dose:

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

ARV-naive patients:

- *Boosted with RTV, twice-daily regimen:* FPV 700 mg + RTV 100 mg, both twice daily.
- *Boosted with RTV, once-daily regimen:* FPV 1400 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.

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 1400 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. Please refer to the package insert.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

Major Toxicities:

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.

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- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.
- *Pediatric specific:* In clinical trials of fosamprenavir, vomiting was more frequent in children than in adults (20%–60% vs. 10%–16%, respectively) as was neutropenia (15% vs. 3%, respectively).[1]

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/APV_FPV.html).

Pediatric Use: Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but the Panel recommends use only for children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this or any other age group because of low exposures and because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.[2]

Dosing recommendations for fosamprenavir are based on 3 pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In 2 open-label trials in both treatment-experienced and treatment-naive children from ages 2 to 18 years;[3, 4] fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.[1] Exposures in those younger than age 6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir. Given these low exposures, limited data, large volumes, unpleasant taste, and the availability of alternatives for infants and young children, the panel does not recommend fosamprenavir use in infants younger than 6 months.

Population	Dose	AUC_{0-24} (mcg*hr/mL) except where noted	C_{min} (mcg/mL)
Infants <6 months	45 mg FPV/10 mg RTV per kg twice daily	26.6[a]	0.86
Children aged 2–<6 years	30 mg FPV per kg twice daily (no RTV)	22.3[a]	0.513
Children weighing <11 kg	45 mg FPV/7 mg RTV per kg twice daily	57.3	1.65
Children weighing 15–<20 kg	23 mg FPV/3 mg RTV per kg twice daily	121.0	3.56
Children weighing ≥20 kg	18 mg FPV/3 mg RTV per kg twice daily (max 700/100)	72.3–97.9	1.98–2.54
Adults	1400 mg FPV twice daily (no RTV)	33	0.35
Adults	1400 mg FPV/100–200 mg RTV once daily	66.4–69.4	0.86–1.45
Adults	700 mg FPV/100 mg RTV twice daily	79.2	2.12

[a] AUC_{0-12} (mcg*hr/mL)

Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies, therefore, area under the curve and C_{min} are not available.

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Indinavir (IDV, Crixivan) (Last updated November 1, 2012; last reviewed November 1, 2012)

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:

- 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 IDV doses (234–500 mg/m^2 of body surface area) boosted by low-dose ritonavir (RTV) have been studied in children (see text).

Adolescent/adult dose:

- 800 mg IDV + 100 or 200 mg RTV 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 RTV, 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 (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.

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Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Metabolism:* CYP3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

Major Toxicities:

- *More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritis, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits.
- *Less common (more severe):* Fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).
- *Pediatric specific:* The cumulative frequency of nephrolithiasis is higher in children (29%) than in adults (12.4%).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/IDV.html).

Pediatric Use: Indinavir has not been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.[1]

Both unboosted and ritonavir-boosted indinavir have been studied in HIV-infected children. Data in children indicate that an unboosted indinavir dose of 500 to 600 mg/m^2 of body surface area given every 8 hours results in peak blood concentrations and area under the curve slightly higher than those in adults but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.[2-5] Studies in small groups of children of a range of ritonavir-boosted indinavir doses have shown that indinavir 500 mg/m^2 of body surface area plus ritonavir 100 mg/m^2 of body surface area twice daily is probably too high,[6] that indinavir 234 to 250 mg/m^2 of body surface area plus low-dose ritonavir twice daily is too low,[7, 8] and that indinavir 400 mg/m^2 of body surface area plus ritonavir 100 to 125 mg/m^2 of body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable interindividual variability and high rates of toxicity.[8-10]

As noted above, the cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%).[11] This is likely due to the difficulty in maintaining adequate hydration in children. Finally, a large analysis of more than 2,000 HIV-infected children from PACTG 219 demonstrated a hazard ratio of 1.7 for risk of renal dysfunction in children receiving antiretroviral therapy with indinavir.[12]

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated November 1, 2012; last reviewed November 1, 2012)

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)

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.

Dosing for individuals not receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV)

Infant dose (14 days–12 months):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r per m^2 of body surface area twice daily.

  NOTE: Use of 300 mg/75 mg LPV/r per m^2 of body surface area in infants aged 12 months 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 text below).

Pediatric dose (>12 months–18 years):

- Once-daily dosing is **not** recommended.
- 300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily is routinely used by many clinicians, especially for patients previously treated with antiretroviral drugs or when decreased sensitivity to LPV is suspected because of clinical history or documented by resistance testing (see text below).
- 230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily can be used 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 patients to "grow

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* below).

Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food, as a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask 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° to 46°F) LPV/r oral solution remains stable until the expiration date printed on the label.

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into" the 230 mg/m^2 dosage as they gain weight over time (see text below). Some would continue the infant dose (300 mg/m^2 of body surface area per dose twice daily) while on LPV/r liquid formulation.

Weight Band Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents		
	Recommended number of 100 mg/25 mg LPV/r 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)		
15–20 kg	2	2
>20–25 kg	3	2
>25–30 kg	3	3
>30–35 kg	4[a]	3
>35–45 kg	4	4
>45 kg	4 or 5[b]	4

[a] Note that 4 of the 100 mg/25 mg LPV/r tablets can be substituted by 2 tablets each containing 200 mg/50 mg LPV/r, but the 200 mg/50 mg LPV/r tablets are bigger and may be difficult to swallow

[b] ***In patients receiving concomitant NVP, EFV, FPV, or NFV***, for body weight >45 kg, the FDA-approved adult 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. Some Panel members would use 600 mg/150 mg LPV/r for ease of dosing.

Adult dose (>18 years):

- 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, or in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV, or in patients with three or more LPV-associated mutations (see *Special Instructions* for list):

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

- The panel generally does not recommend once-daily dosing of LPV/r for children aged <18 years because of high variability of its metabolism in children.
- Do not use once daily if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- Cytochrome P (CYP) 3A4 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 enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

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- 400 mg/100 mg LPV/r twice daily.

Dosing 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.)*

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

Pediatric dose (>12 months to 18 years):

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

Adult dose (>18 years):

- 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* CYP450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. Fluticasone, a commonly used inhaled and intranasal steroid, should not be used in patients treated with lopinavir/ritonavir.

Major Toxicities:

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia
- *Less common (more severe):* Fat maldistribution
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases). PR interval prolongation. QT interval prolongation and torsade de pointes may occur. Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants

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because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency,[1] life-threatening bradyarrhthymias and cardiac dysfunction,[2-4] and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression.[4] These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%.[4] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir.[1]

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/LPV.html).

Pediatric Use:

Lopinavir/ritonavir is FDA-approved for use in children. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

There is some controversy about the dosing of lopinavir/ritonavir in children. Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m^2. For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per m^2. However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C_{trough} to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area.

A PK study in 12 children aged 6 months to 12 years receiving 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 4.74 ± 2.93 mcg/mL (about 67% of the adult value of 7.1 ± 2.9 mcg/mL).[5] For 15 children ages 6 months to 12 years treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 7.91 ± 4.52 mcg/mL, similar to that in adults treated with 400 mg/100 mg lopinavir/ritonavir twice daily.[5] In a study of 23 children (median age 5.6 years; range 0.4 to 13 years) treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), mean lopinavir area under the curve (AUC) and C_{min} were lower than that observed in adults treated with 400/100 mg lopinavir/ritonavir twice daily.[6] Lopinavir C_{min} <1.0 mg/L was found in 7 of 23 participants: 5 of 7 in the age group <2 years, and 2 of 16 children aged 2 years or older ($P = 0.01$).[6] Therefore, some clinicians choose to initiate therapy in children ages 6 months to 12 years using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug label-recommended 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily.

The PK of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily was evaluated in infants younger than age 6 weeks[7] and infants aged 6 weeks to 6 months.[8] Lopinavir exposures from these studies are compared to those in older children[5] and adults[9] as shown in the table below. Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

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	Adults[9]	Children[5]	Children[5]	Infants at 12 months[10] [a]	Infants 6 weeks–6 months[8]	Infants <6 weeks[7]
N	19	12	15	20	18	9
Dose LPV	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC mcg-hr/mL	92.6	72.6	116.0	101.0	74.5	43.4
C_{max} mcg/mL	9.8	8.2	12.5	12.1	9.4	5.2
C_{trough} mcg/mL	7.1	4.7	7.9	4.9	2.7	2.5
C_{min} mcg/mL	5.5	3.4	6.5	3.8	2.0	1.4

[a] Data generated in study cited but not reported in final manuscript; data in table according to an e-mail from Edmund Capparelli, PharmD (April 18, 2012)

Even at this higher dose, pre-dose (C_{trough}) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants aged 6 weeks or younger compared with those ages 6 weeks to 6 months. By age 12 months, lopinavir AUC was similar to that found in older children.[10] Because infants gain weight rapidly in the first months of life, one important way to optimize lopinavir dosing is to weigh a patient and adjust the dose for growth at frequent intervals. Given the safety of doses as high as 400 mg/m^2 body surface area in older children and adolescents,[11] some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m^2 body surface area dose to let the infant "grow into" the 300 mg/m^2 body surface area amount.

In both children and adults the lopinavir C_{trough} is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors or concomitant fosamprenavir or nelfinavir and higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL.[5] For 12 children treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily, the mean C_{trough} was 5.62 ± 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than adults.[5, 6] In a study of 15 HIV-infected children treated with the combination of lopinavir/ritonavir using an increased dose of 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, the median 12-hour lopinavir trough was 5.7 mcg/mL, but there was 34-fold inter-individual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.[12] A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/75 mg per m^2 of body surface area twice daily plus efavirenz 350 mg/m^2 of body surface area once daily showed adequacy of the lopinavir trough values.[13]

Once-daily dosing of lopinavir/ritonavir 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV infection in therapy-naive adults older than age 18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM) because of high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21 (35.6%) of 59 patients.[14-17] Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower

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variability in trough levels,[17, 18] but the Panel remains concerned about the long-term effectiveness of once-daily lopinavir/ritonavir in children.

Lopinavir/ritonavir has been shown to be effective as salvage therapy in HIV-infected children with severe immune suppression,[19, 20] although patients with greater prior exposure to antiretrovirals may have slower reductions in virus load to undetectable concentrations[20, 21] and less robust response in CD4 percentage.[22] Twice daily doses of lopinavir used in this cohort were 230 to 300 mg/m^2 of body surface area in 39% of patients, 300 to 400 mg/m^2 of body surface area in 35%, and greater than 400 mg/m^2 of body surface area per dose in 4%.[22]

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just before a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC_{50}). The ratio of C_{trough} to EC_{50} is called the inhibitory quotient (IQ), and in both adults and children treated with lopinavir/ritonavir, virus load reduction is more closely associated with IQ than with either the C_{trough} or EC_{50} alone.[23-26] A study of the practical application of the IQ to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (with nevirapine or efavirenz).[11] Results of a modeling study suggest that standard doses of lopinavir/ritonavir are likely to be inadequate for treatment-experienced children and underscore the potential utility of TDM in children previously treated with protease inhibitors and now on salvage therapy with lopinavir/ritonavir.[27]

Lopinavir/ritonavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C_{max}, and C_{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.[28] In a PK study using a generic adult formulation of lopinavir/ritonavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C_{trough} measurements.[18]

Compared with children treated with NNRTI-based regimens, those treated with lopinavir/ritonavir may have less robust weight gain and smaller increases in CD4 percentage.[29-31] The poor weight gain associated with lopinavir/ritonavir is not understood.

The poor palatability of the oral solution can be a significant challenge to medication adherence for some children and families. Numbing of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods, chocolate syrup, or peanut butter, for example, or by flavoring the solution by the pharmacist prior to dispensing, are examples of interventions that may improve tolerability.

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Nelfinavir (NFV, Viracept) (Last updated November 1, 2012; last reviewed November 1, 2012)

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:

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

Pediatric dose (2–13 years of age):

- 45–55 mg/kg twice daily.

Adolescent/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 NFV with meal or light snack.
- If co-administered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, ritonavir boosting does not significantly increase nelfinavir concentrations and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir.

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- Before administering nelfinavir, carefully review a patient's medication profile for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea (most common), asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NFV.html).

Pediatric Use: Nelfinavir is a protease inhibitor (PI) that has been used in combination with 2 nucleoside reverse transcriptase inhibitors in children aged >2 years. Nelfinavir is not recommended for treatment in children aged <2 years (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 prevention of mother-to-child transmission of HIV*).

Nelfinavir in combination with other antiretroviral drugs has been extensively studied in HIV-infected children.[1-8] In randomized trials of children ages 2 to 13 years receiving nelfinavir as part of triple antiretroviral therapy (ART), the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior history of ART, the number of drugs included in the combination regimen, and dose of nelfinavir used. The relatively poor ability of nelfinavir to control plasma viremia in infants and children may be related in part to the ARV's reduced potency compared with other PIs or non-nucleoside reverse transcriptase inhibitors as well as highly variable drug exposure, metabolism, and poor patient acceptance of available formulations.[9-11]

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increased by as much as five fold) and decreases pharmacokinetic (PK) variability relative to the fasted state. Drug exposure may be even more unpredictable in pediatric patients than in adults because of increased clearance of nelfinavir observed in children, and difficulties in taking nelfinavir with sufficient food to improve bioavailability. A pediatric powder formulation, no longer available, was poorly tolerated when mixed with food or formula. In the PENTA-7 trial, 35% (7 of 20) of infants started on powder at initiation of therapy were switched from the powder to crushed tablets because of difficulty administering the oral formulation to the infants.[1] A slurry made by dissolving nelfinavir tablets in water or other liquids can be administered to children who are unable to swallow tablets. The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.[12]

Nelfinavir is metabolized by multiple CYP-450 enzymes including CYP3A4 and CYP2C19. M8, the major oxidative metabolite, has *in vitro* antiviral activity comparable to the parent drug. The variability of drug exposure at any given dose is much higher for children than adults,[13] which has been attributed at least in part to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children.[14, 15] Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir PKs and the virologic responses to combination therapy in HIV-1-infected children. These findings

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suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in HIV-1-infected children.[9]

Antiviral response to nelfinavir is significantly less in children younger than age 2 years than in older children.[6, 8, 16] Infants have even lower drug exposures and higher variability in plasma concentrations than children <25 kg; the presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors.[17, 18] For these reasons, nelfinavir is not recommended for use in children younger than 2 years of age. In older children and adolescents, it is unclear when to change from the recommended 45 to 55 mg/kg twice-daily dose to the adult dose of 1250 mg twice daily. Doses higher than those recommended in adults may be required in some patients.

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{min}) <1.0 mcg/mL.[19-21] In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough <0.8 mcg/mL.[22] It is of note that the median age of the group with C_{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} >0.8 mcg/mL was 8.3 years.[22] Therapeutic drug monitoring (TDM) of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir.[19, 23] Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of TDM and appropriate dose adjustment may be even greater for children. Better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing.[15, 24]

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Ritonavir (RTV, Norvir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 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 protease inhibitors (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
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

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.
- 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.

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To increase tolerability of RTV 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, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P (CYP)3A4 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 unavailable 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions with ritonavir.
- Before ritonavir is administered, a patient's medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.
- Avoid concomitant use of intranasal or inhaled fluticasone. Use caution when prescribing ritonavir with other inhaled steroids because of reports of adrenal insufficiency.[1-3]

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.

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Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[4]

Resistance: Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs).

Pediatric Use: Ritonavir has been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Use of ritonavir as the sole PI in antiretroviral therapy (ART) in children is not recommended. However, in both children and adults, ritonavir is recommended as a PK enhancer to boost another/second PI in an ART regimen. Ritonavir acts by inhibiting the metabolism of the second (boosted) PI in the regimen, thereby increasing the plasma concentration of the second/boosted PI. Lopinavir/ritonavir, a PI coformulation, has been well studied in children and is a preferred PI for therapy in children (see Lopinavir/Ritonavir). Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, and atazanavir are available (see individual PIs for more specific information).

Although ritonavir has been well studied, its use in children as a sole PI for therapy is limited because ritonavir is associated with a higher incidence of GI toxicity and has a greater potential for drug-drug interactions than other PIs. Also, ritonavir as a sole PI is associated with a higher risk of virologic failure than efavirenz or lopinavir/ritonavir.[5-7] In addition, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules or tablets twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than 2 years, and doses of 350 to 450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group.[8-19]

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily.[4] Potentially life-threatening arrhythmias in premature newborn infants treated with lopinavir/ritonavir have been reported; thus, lopinavir/ritonavir should not be used in this group of patients.[20, 21] Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as those with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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Saquinavir (SQV, Invirase) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Hard-gel capsules: 200 mg

Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

- Not approved for use in children.

Investigational doses in treatment-experienced children:

- SQV must be boosted with ritonavir (RTV):

Aged <2 years:

- No dose has been determined.

Aged ≥2 years (conditional dosing based on limited data, see text):

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

Aged ≥7 years in combination with lopinavir/ritonavir (LPV/r) for salvage therapy (conditional dosing based on limited data, see text):

- SQV 750 mg/m^2 (max 1600 mg) or SQV 50 mg/kg have been used in combination with LPV/r, both twice daily.

Adolescent (aged ≥16 years)/adult dose:

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

- SQV 1000 mg + RTV 100 mg, both twice daily.
- SQV 1000 mg + LPV/r 400/100 mg, both twice daily.

Selected Adverse Events

- Gastrointestinal 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 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 (ECG) is recommended and SQV is not recommended in patients with a prolonged QT interval.

Metabolism

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

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Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Metabolism:* Saquinavir is both a substrate and inhibitor of the CYP3A4 system, and there is potential for numerous drug interactions.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and torsades de pointes.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/SQV.html).

Pediatric Use: Saquinavir is not Food and Drug Administration (FDA)-approved for use in children. Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors (PIs) in HIV-infected children.[1-6] Initial studies suggest that saquinavir should not be used without boosting by ritonavir or lopinavir/ritonavir. A pharmacokinetic (PK) analysis of 5 children aged younger than 2 years and 13 children aged 2 to 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir demonstrated that drug exposure was lower in children younger than age 2 years whereas drug exposure was adequate in those ages 2 to 5 years.[7] For this reason, saquinavir should not be given to children younger than age 2 years until an appropriate dose is identified. In children aged ≥2 years, a dose of 50 mg/kg twice daily (maximum dose = 1000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 – <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 – 40 kg) resulted in area under the curve and steady state trough concentration (C_{trough}) values similar to those in older children[8, 9] and adults. Because there is no pediatric formulation, in one study saquinavir was formulated by breaking open the 200-mg hard-gel capsules and mixing capsule contents with sugar syrup, jam, or baby formula. Sorbitol syrup was used for patients with diabetes or glucose intolerance.[7]

Both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens are promising for salvage therapy in children.[1, 3-6, 8-10] In a study evaluating the addition of saquinavir (750 mg/m^2 of body surface area every 12 hours, maximum dose 1600 mg) to a regimen containing lopinavir/ritonavir dosed at 400/100 mg/m^2 of body surface area twice daily (for patients not concurrently taking a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or lopinavir/ritonavir 480/120 mg/m^2 of body surface area twice daily for patients concurrently administered an NNRTI, 18 subjects (median age 14.2 years, range 7.7–17.6 years) were enrolled. The addition of saquinavir at these doses was well tolerated and did not appear to alter lopinavir PKs. Saquinavir dosing was adjusted in four patients (decreased in three, increased in one).[10]

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance. In this group, saquinavir was dosed at 50 mg/m^2 of body surface area and lopinavir/ritonavir was dosed at 230/57.5 mg/m^2 of body surface area, all twice daily. After 96 weeks of

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treatment, 74% of the children achieved an undetectable plasma RNA load at <50 copies/mL. Therapeutic drug monitoring was used to establish adequate minimum plasma concentration (C_{min}) values and to aid with alterations in drug dosage based upon toxicity. Most C_{min} values for saquinavir were above the desired trough value of 0.1 mg/L. The average C_{min} throughout 96 weeks for saquinavir was 1.37 mg/L, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8 mg/kg). Median total cholesterol and high-density lipoprotein values increased significantly through 96 weeks from 144 to 196 mg/dL and from 44 to 57 mg/dL, respectively.[8, 9]

In a healthy adult volunteer study, saquinavir/ritonavir use was associated with increases in both QT and PR intervals.[11] The degree of QT prolongation was greater than that seen with some other boosted PIs. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Saquinavir/ritonavir is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval. An electrocardiogram is recommended before initiation of therapy with saquinavir and should be considered during therapy.

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Tipranavir (TPV, APTIVUS) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 (aged <2 years):

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

Pediatric dose (2–18 years of age):

Not recommended for treatment-naive patients.

- *Body surface area dosing:*
  TPV 375 mg/m^2 + RTV 150 mg/m^2, 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:

Not recommended for treatment-naive patients.

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

Selected Adverse Events

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

Special Instructions

- Administer TPV and RTV together with food.
- TPV 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.
- TPV contains a sulfonamide moiety 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 unopened bottles of oral TPV capsules in a refrigerator at 2° to 8°C (36°–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 TPV with caution in patients who may be at risk of increased bleeding from trauma,

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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 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- Tipranavir has the potential for multiple drug interactions.
- Before tipranavir is administrated, a patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities:

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Elevated transaminases, cholesterol, and triglycerides.
- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage.

Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TPV.html).

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Pediatric Use: Tipranavir is Food and Drug Administration (FDA) approved for use in children aged ≥2 years who are treatment-experienced and infected with HIV strains resistant to more than one protease inhibitor (PI).[1] The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the burden of taking a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events that limit its use to patients with few treatment options. However, tipranavir is approved for use in children as young as age 2 years and is available in a liquid formulation.

FDA approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of tipranavir/ritonavir in HIV-infected children (PACTG 1051/BI-1182.14).[2] This study enrolled treatment-experienced children (with the exception of 3 treatment-naive patients) ages 2 to 18 years (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children in 3 age strata were randomized to 2 different doses of tipranavir/ritonavir: tipranavir/ritonavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg/m^2 body surface area (high dose, 57 patients) twice daily, plus optimized background therapy. All children initially received the oral solution but patients who were aged 12 years or older and receiving the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily were eligible to switch to tipranavir capsules after Week 4. At baseline, resistance to all commercially available PIs was present in greater than 50% of patient isolates, and the tipranavir/ritonavir mutation scores increased with age.[2] At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of those receiving the high dose had viral loads <400 copies/mL. The groups did not differ in percentage of patients who achieved viral loads <50 copies/mL. The proportion of patients with HIV RNA levels <400 copies/mL tended to be greater in the youngest patients (70%) who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 T lymphocyte count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, adverse effects were similar between treatment groups. Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs because of adverse events. The most common adverse events were gastrointestinal disturbances; 37% of participants had vomiting and 24% had diarrhea. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase and creatine phosphokinase) was seen in 11% of children. Four patients (all in the low-dose group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus high-dose group reached statistical significance ($P = 0.04$). In a multivariate model, three variables (listed in order) predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100,000 copies/mL. GIQ is calculated by dividing the tipranavir trough concentration by the number of tipranavir resistance-conferring mutations genotyped from a patient's HIV strain. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, high-dose tipranavir/ritonavir has been recommended.

PKs of the liquid formulation at steady state were assessed.[3] In children ages 2 to <12 years, at a dosage of tipranavir/ritonavir 290/115 mg/m^2 body surface area, tipranavir trough concentrations were consistent with those achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children ages 12 to 18 years required a higher dose (375/150 mg/m^2 body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard tipranavir/ritonavir dose. Population PK analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age.[3] Based on these studies, the final dose of tipranavir/ritonavir 375/150 mg/m^2 body surface area twice daily is recommended.

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Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir/mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/kg body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%).[2] Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.[4]

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Appendix A: Pediatric Antiretroviral Drug Information

Entry and Fusion Inhibitors

Enfuvirtide (ENF, T-20, Fuzeon)

Maraviroc (MVC, Selzentry)

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Enfuvirtide (ENF, T-20, Fuzeon) (Last updated August 11, 2011; last reviewed November 1, 2012)

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 (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 into the upper arm, anterior thigh, or abdomen.

Adolescent (aged >16 years)/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. Re-challenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous (SQ) injections. ENF 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 ENF immediately or keep refrigerated in the original vial until use. Reconstituted ENF must be used within 24 hours.
- ENF 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

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to better disperse the dose. There are reports of injection-associated neuralgia and parasthesia 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.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- There are no known significant drug interactions with enfuvirtide.

Major Toxicities:

- *More common:* Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association).
- *Rare:* Hypersensitivity reactions (HSRs) (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.
- *Pediatric specific:* Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).[1]

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ENF.html).

Pediatric Use: Although enfuvirtide is Food and Drug Administration (FDA) approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens[2] has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

A single-dose pharmacokinetic (PK) evaluation study of enfuvirtide given SQ to 14 HIV-infected children aged 4 to 12 years (PACTG 1005) identified that enfuvirtide 60 mg/m^2 of body surface area per dose resulted in a target trough concentration that approximated the "equivalent" of a 90-mg dose delivered SQ

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to an adult (1,000 mg/mL).[3] In a second pediatric study of 25 children aged 5 to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily yielded drug concentrations similar to 60 mg/m^2 of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.[4] The FDA-recommended dose of enfuvirtide for children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m^2 per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a >1.0 log reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively.[5] However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at Week 96. Most children had local injection site reactions.[6] Significant improvements in CD4 percentage and height *z* score were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase I/II study of enfuvirtide (2.0 mg/kg SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and increase in CD4 T lymphocyte (CD4 cell) count was 106 cells/mm^3 (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm^3 in children and 84 cells/mm^3 in adolescents. Local skin reactions were common in all age groups (87% of study participants). The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen.[1]

An increased rate of bacterial pneumonia was observed in adults treated with enfuvirtide in some studies (FDA) but not in others.[7] Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.

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Maraviroc (MVC, Selzentry) (Last updated November 1, 2012; last reviewed November 1, 2012)

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 <16 years.
- A pediatric clinical trial is under way

Adolescent (aged >16 years)/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
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
When given with potent CYP3A inducers including efavirenz (EFV) and etravirine (ETR) (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 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.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism

- 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,

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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

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Absorption:* Absorption of maraviroc is somewhat reduced with ingestion of a high-fat meal; however, maraviroc can be given with or without food.
- *Metabolism:* Maraviroc is a CYP3A4 and p-glycoprotein (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with maraviroc.

Major Toxicities:

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.
- *Less common (more severe):* Hepatotoxicity that may be preceded by evidence of a systemic allergic reaction (such as pruritic rash, eosinophilia or elevated immunoglobulin [IgE]) has been reported. Serious adverse events occurred in less than 2% of maraviroc-treated adult patients and included cardiovascular abnormalities (such as angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html). Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Use: The pharmacokinetics (PK), safety, and efficacy of maraviroc in patients aged <16 years have not been established. A dose-finding study is under way in children aged 2 to 17 years.[1] In this trial, maraviroc dose is based upon body surface area and the presence or absence of a potent CYP3A4 inhibitor in the background regimen. Preliminary PK data are encouraging in those on a potent CYP3A4 inhibitor, but exposures are very low in those not on a potent CYP3A4 inhibitor.

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Appendix A: Pediatric Antiretroviral Drug Information

Integrase Inhibitors

Raltegravir (RAL, Isentress)

Elvitegravir (EVG)

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Raltegravir (RAL, Isentress) (Last updated November 5, 2012; last reviewed November 1, 2012)

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
* Film-coated tablets and chewable tablets are not interchangeable.

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

Children aged 2 to <12 years:

- <25 kg: Chewable tablet twice daily to maximum of 300 mg twice daily (see table)
- ≥25 kg: 400 mg film-coated tablet twice daily OR chewable tablets (see table)

Dosing of chewable tablets in children aged 2 to <12 years of age

Body Weight (kg)	Dose	Number of Chewable Tablets
10 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 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

Adolescent (≥12 years of age)/adult dose:

- 400 mg film-coated tablet twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.
- Film-coated tablets and chewable tablets are not interchangeable. Chewable tablets have better bioavailability than the film-coated tablets. Chewable tablets should be stored in the original package with desiccant to protect from moisture.

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 necessary.

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Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Metabolism:* The major route of raltegravir elimination is mediated through glucuronidation by UGT1A1.
- Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Efavirenz and etravirine may decrease raltegravir concentrations.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting, insomnia. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than are patients who are not coinfected.
- *Rare:* Creatine phosphokinase elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. Thrombocytopenia.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/cgi-bin/INIResiNote.cgi).

Pediatric Use: Raltegravir is approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years. Raltegravir has been studied in 126 antiretroviral (ARV) treatment-experienced HIV-1-infected children and adolescents aged 2 to 18 years in combination with an optimized background ARV regimen in IMPAACT P1066. Additional experience from the French expanded access program in treatment-experienced adolescents support the good virologic and immunologic results observed in P1066.[1, 2]

IMPAACT P1066 is a Phase I/II open label multicenter study to evaluate the pharmacokinetic (PK) profile, safety, tolerability, and efficacy of various formulations of raltegravir in HIV-infected children. Subjects received either the 400-mg film-coated tablet formulation twice daily (patients aged 6–18 years and weighing at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). Current pediatric approval and dosing recommendations are based upon these evaluations in 96 patients.[3-7]

In IMPAACT P1066, the initial dose-finding stage includes intensive PK evaluation in various age cohorts: (aged 12 to <19 years, 6 to <12 years, 2 to <6 years). Dose selection was based upon achieving target PK parameters similar to those seen in adults: PK targets are geometric mean (GM) area under the curve of 14-25 µMxh and GM 12 h concentration >33 nM. Additional subjects were then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. Ninety-three (97%) subjects completed 24 weeks of treatment with 54% achieving HIV RNA <50 copies/mL with a mean CD4 T lymphocyte count (percent

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[%]) increase of 119 cells/mm^3 (3.8%). The frequency, type, and severity of drug-related adverse reactions through week 24 were comparable to those observed in adult studies. Observed adverse reactions considered drug-related included one patient with grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient with a grade 2 allergic rash; and one patient with grade 3 ALT and grade 4 AST laboratory elevations.

The investigational raltegravir oral granules for suspension formulation are currently under study in P1066 in children aged 4 weeks to <2 years. Recent data, obtained from 9 children aged 6 months to <2 years, suggest that the oral granules are well tolerated with favorable preliminary efficacy. PK data obtained in 8 of the 9 young children achieved targets similar to those observed in the 2- to 11-year-olds receiving the chewable tablets.[8] A dosage of 6 mg/kg every 12 hours was chosen for continued study in this age group.

The raltegravir chewable tablet has higher oral bioavailability than the film-coated tablet based on a comparative study in healthy adult volunteers.[9] In the PK of raltegravir, interpatient and intrapatient variability is considerable.[10]

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Elvitegravir (EVG) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Only available in fixed-dose combination tablets (Stribild):

Elvitegravir (EVG) + cobicistat (COBI) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF)

EVG 150 mg + COBI 150 mg + FTC 200 mg + TDF 300 mg

Dosing Recommendations

Pediatric dose (aged <18 years):

- Not FDA-approved or -recommended for use in children aged <18 years.

Adult dose (aged ≥18 years):

- 1 tablet once daily in antiretroviral (ARV) treatment-naive adults.

Selected Adverse Events

- Diarrhea, nausea, flatulence
- Renal insufficiency
- Cobicistat alters tubular secretion of creatinine, and therefore, may decrease creatinine-based estimates of glomerular filtration rate without a true change in glomerular filtration.
- Decreased bone mineral density (BMD)

Special Instructions

- Administer with food.
- Monitor estimated creatinine clearance, urine glucose, and urine protein; 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 FTC or TDF. Severe acute exacerbation of HBV can occur when FTC or TDF are discontinued; therefore, monitor hepatic function for several months after therapy with FTC or TDF is stopped.
- Not recommended for use with other ARV drugs.

Metabolism

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

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Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Metabolism:* Stribild contains elvitegravir and cobicistat. Elvitegravir is metabolized by cytochrome P (CYP) 3A4 and is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, it inhibits ATP-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided.
- *Protease inhibitors (PIs):* Stribild should not be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A.
- Not recommended for use with other ARV drugs.

Major Toxicities:

- *More common:* Nausea, diarrhea, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors including tenofovir disoproxil fumarate (tenofovir) and emtricitabine. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been reported in both adults and children taking tenofovir; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Pediatric Use: Elvitegravir is only available as the fixed-dose combination product Stribild, which contains elvitegravir/cobicistat/emtricitabine/tenofovir. Stribild is not U.S. Food and Drug Administration (FDA)-approved for use in children aged <18 years. There are no data on its use in individuals aged <18 years.

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor added as a pharmacokinetic enhancer. Cobicistat slows elvitegravir metabolism and allows once-daily administration of the combination. Stribild is FDA-approved as a complete ARV regimen in HIV-1-infected ARV-naive adults aged ≥18 years[1] based on trials showing non-inferiority to regimens of emtricitabine/tenofovir plus atazanavir/ritonavir,[2] or emtricitabine/tenofovir plus efavirenz.[3] There is cross-resistance between elvitegravir and raltegravir.[4] Cobicistat alters the renal tubular secretion of creatinine, so creatinine-based calculations of estimated glomerular filtration rate will be altered, even though the actual glomerular filtration rate might be only minimally changed.[5] Adults who experience a confirmed increase in serum creatinine greater than 0.4 mg/dL from baseline should be closely monitored for renal toxicity.[1]

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