Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 2/21/2013 EST.

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.

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.

- 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

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 bradyarrhythmias 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).

	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

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.

References

1. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. Jul 6 2011;306(1):70-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/21730243.
2. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS*. Nov 30 2007;21(18):2564-2565. Available at http://www.ncbi.nlm.nih.gov/pubmed/18025905.

3. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J*. Dec 2009;28(12):1127-1129. Available at http://www.ncbi.nlm.nih.gov/pubmed/19820426.
4. Boxwell D, K. Cao, et al. Neonatal Toxicity of Kaletra Oral Solution—LPV, Ethanol, or Propylene Glycol?- Abstract #708. 18th Conference on Retroviruses and Opportunistic Infections (CROI). Boston MA. 2011.
5. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. Mar 2003;22(3):216-224. Available at http://www.ncbi.nlm.nih.gov/pubmed/12634581.
6. Verweel G, Burger DM, Sheehan NL, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir Ther*. 2007;12(4):453-458. Available at http://www.ncbi.nlm.nih.gov/pubmed/17668553.
7. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J*. Mar 2009;28(3):215-219. Available at http://www.ncbi.nlm.nih.gov/pubmed/19209098.
8. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS*. Jan 11 2008;22(2):249-255. Available at
9. Food and Drug Administration (FDA). Lopinavir-ritonavir (Kaletra) product label. 2010; http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021226s030lbl.pdf.
10. Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*. Mar 13 2011;25(5):643-649. Available at http://www.ncbi.nlm.nih.gov/pubmed/21297419.
11. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother*. Sep 2008;52(9):3276-3283. Available at http://www.ncbi.nlm.nih.gov/pubmed/18625762.
12. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr*. May 1 2005;39(1):63-68. Available at http://www.ncbi.nlm.nih.gov/pubmed/15851915.
13. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J*. Feb 2009;28(2):159-161. Available at http://www.ncbi.nlm.nih.gov/pubmed/19106779.
14. Rosso R, Di Biagio A, Dentone C, et al. Lopinavir/ritonavir exposure in treatment-naive HIV-infected children following twice or once daily administration. *J Antimicrob Chemother*. Jun 2006;57(6):1168-1171. Available at http://www.ncbi.nlm.nih.gov/pubmed/16606636.
15. van der Lee M, Verweel G, de Groot R, Burger D. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther*. 2006;11(4):439-445. Available at http://www.ncbi.nlm.nih.gov/pubmed/16856617.
16. la Porte C, van Heeswijk R, Mitchell CD, Zhang G, Parker J, Rongkavilit C. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther*. 2009;14(4):603-606. Available at http://www.ncbi.nlm.nih.gov/pubmed/19578247.
17. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther*. 2008;13(8):1087-1090. Available at http://www.ncbi.nlm.nih.gov/pubmed/19195335.
18. Puthanakit T, Chokephaibulkit K, Suntarattiwong P, et al. Therapeutic drug monitoring of lopinavir in human

immunodeficiency virus-infected children receiving adult tablets. *Pediatr Infect Dis J*. Jan 2010;29(1):79-82. Available at http://www.ncbi.nlm.nih.gov/pubmed/19858772.

19. Resino S, Bellon JM, Ramos JT, et al. Salvage lopinavir-ritonavir therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. Oct 2004;23(10):923-930. Available at http://www.ncbi.nlm.nih.gov/pubmed/15602192.
20. Resino S, Bellon JM, Munoz-Fernandez MA, Spanish Group of HIVI. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother*. Mar 2006;57(3):579-582. Available at http://www.ncbi.nlm.nih.gov/pubmed/16446377.
21. Resino S, Galan I, Perez A, et al. Immunological changes after highly active antiretroviral therapy with lopinavir-ritonavir in heavily pretreated HIV-infected children. *AIDS Res Hum Retroviruses*. May 2005;21(5):398-406. Available at http://www.ncbi.nlm.nih.gov/pubmed/15929702.
22. Larru B, Resino S, Bellon JM, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. *J Antimicrob Chemother*. Jan 2008;61(1):183-190. Available at http://www.ncbi.nlm.nih.gov/pubmed/18025025.
23. Casado JL, Moreno A, Sabido R, et al. Individualizing salvage regimens: the inhibitory quotient (C_{trough}/IC50) as predictor of virological response. *AIDS*. Jan 24 2003;17(2):262-264. Available at http://www.ncbi.nlm.nih.gov/pubmed/12545089.
24. Delaugerre C, Teglas JP, Treluyer JM, et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. *J Acquir Immune Defic Syndr*. Oct 1 2004;37(2):1269-1275. Available at http://www.ncbi.nlm.nih.gov/pubmed/15385734.
25. Havens P, Frank M, Cuene B, al e. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m^2/dose in children and adolescents with HIV infection. 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA.
26. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. Jan 2003;47(1):350-359. Available at http://www.ncbi.nlm.nih.gov/pubmed/12499212.
27. Rakhmanina N, van den Anker J, Baghdassarian A, Soldin S, Williams K, Neely MN. Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. Jun 2009;53(6):2532-2538. Available at http://www.ncbi.nlm.nih.gov/pubmed/19258274.
28. Diep H, Best B, Capparelli E, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. Abstract #877. Conference on Retroviruses and Opportunistic Infections (CROI) Feb 27-Mar 2, 2010, San Francisco, CA.
29. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. Sep 8 2010;304(10):1082-1090. Available at http://www.ncbi.nlm.nih.gov/pubmed/20823434.
30. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. Oct 14 2010;363(16):1510-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/20942667.
31. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. Jun 21 2012;366(25):2380-2389. Available at http://www.ncbi.nlm.nih.gov/pubmed/22716976.