Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 16, 2019; last reviewed April 16, 2019)

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**Formulations**

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

**Film-Coated Tablets:**
- [**Kaletra**] Lopinavir 100 mg/ritonavir 25 mg
- [**Kaletra**] Lopinavir 200 mg/ritonavir 50 mg

**Dosing Recommendations**

**Neonatal (Aged <14 Days) Dose:**
- There are no data on the appropriate dose of lopinavir/ritonavir (LPV/r) for neonates and no data on the safety of using this drug combination in this age group. **Do not administer** LPV/r to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days due to the risk of toxicities.

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

**Infant (Aged 14 Days–12 Months) Dose:**
- Once-daily dosing is **not recommended**.
- LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. **Note:** Use of this dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m² dose.

**Child and Adolescent Dose (Aged >12 Months to 18 Years):**
- Once-daily dosing is **not recommended**.
- LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥15 kg to 45 kg, this dose...

**Selected Adverse Events**

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

**Special Instructions**

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets.**
- LPV/r oral solution should be administered with food, because a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- LPV/r oral solution can be kept at room temperature (up to 77°F or 25°C) if used within 2 months. If kept refrigerated (36°F to 46°F or 2°C to 8°C), LPV/r oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing is not recommended because of considerable variability in plasma...
approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

• LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose should not be used in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

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

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Recommended Number of LPV/r 100 mg/25 mg Tablets Given Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg to 20 kg</td>
<td>300 mg/m²/dose given twice daily (2 tablets)</td>
</tr>
<tr>
<td>&gt;20 kg to 25 kg</td>
<td>230 mg/m²/dose given twice daily (2 tablets)</td>
</tr>
<tr>
<td>&gt;25 kg to 30 kg</td>
<td>300 mg/m²/dose given twice daily (3 tablets)</td>
</tr>
<tr>
<td>&gt;30 kg to 35 kg</td>
<td>300 mg/m²/dose given twice daily (4 tablets)</td>
</tr>
<tr>
<td>&gt;35 kg to 45 kg</td>
<td>300 mg/m²/dose given twice daily (4 tablets)</td>
</tr>
<tr>
<td>&gt;45 kg</td>
<td>300 mg/m²/dose given twice daily (4 tablets)</td>
</tr>
</tbody>
</table>

a Two tablets that each contain LPV/r 200 mg/50 mg can be substituted for the four LPV/r 100 mg/25 mg tablets in children who are capable of swallowing a larger tablet.

b In patients who weigh >45 kg and who are receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, the Food and Drug Administration (FDA)-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

Adult (Aged >18 Years) Dose:

• LPV/r 800 mg/200 mg once daily, or
• LPV/r 400 mg/100 mg twice daily
• Do not use once-daily dosing in children; adolescents; in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir; or in patients with three or more lopinavir-associated concentrations in children aged <18 years and a higher incidence of diarrhea.

• Use of LPV/r once daily is contraindicated if three or more of the following lopinavir resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher lopinavir trough concentrations may be required to suppress resistant virus.

**Metabolism/Elimination**

• Cytochrome P450 3A4 substrate and inhibitor.

**LPV/r Dosing in Patients with Hepatic Impairment:**

• LPV/r is primarily metabolized by the liver. Use caution when administering lopinavir 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 ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.
Drug Interactions: Lopinavir/ritonavir (LPV/r) is a cytochrome P450 3A4 (CYP3A4) substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease lopinavir plasma concentrations, while coadministering LPV/r with other CYP3A4 inhibitors may increase lopinavir plasma concentrations. Coadministering LPV/r with other CYP3A4 substrates may require dose adjustments and additional monitoring.

Before initiating therapy with LPV/r, a patient’s medication profile should be carefully reviewed for potential drug interactions. In patients treated with LPV/r, fluticasone (a commonly used inhaled and intranasal steroid) should be avoided, and an alternative steroid should be used. Drug interactions with anti-tuberculous drugs are common and may require dose adjustments or a regimen change.

Major Toxicities

- More common: Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance. Hyperlipidemia, especially hypertriglyceridemia, which may be more pronounced in girls than in boys. The higher dose of ritonavir used to boost lopinavir, compared with the dose used with some other mutations (see Special Instructions for a list of mutations).

Dosing for Individuals with Three or More Lopinavir-Associated Mutations (See Special Instructions for List):
• LPV/r 400 mg/100 mg twice daily

Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:
• Note: These drugs induce lopinavir metabolism and reduce lopinavir plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing should not be used in these patients.

Child and Adolescent (Aged >12 Months to 18 Years) Dose:
• LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult (Aged >18 Years) Dose:
• The FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing should not be used.

LPV/r Used in Combination with Maraviroc:
• Maraviroc doses may need modification (see the maraviroc section for more information).
protease inhibitors, may exacerbate these adverse events.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, hepatitis (which has been life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur.

- **Special populations—neonates:** An increased risk of toxicity in premature infants has been reported, including cases of transient symptomatic adrenal insufficiency, life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. 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%. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported in term newborns treated at birth with LPV/r. The pharmacokinetics (PKs) and safety of LPV/r were studied in IMPAACT P1106, an opportunistic, multi-arm, Phase 4 prospective study in newborns who received antiretroviral (ARV) and anti-tuberculosis medicines in clinical care. In 25 neonates with HIV who received LPV/r solution at a dose of 300 mg/75 mg per m² twice daily, LPV/r was well tolerated and was not associated with any treatment-related adverse events, even in 13 newborns who initiated therapy prior to 42 weeks postmenstrual age at a mean postnatal age of 37 days (with a range of 13 days–61 days).

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

**Pediatric Use**

**Approval**

LPV/r is approved by the Food and Drug Administration (FDA) for use in children, including in neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, if no alternatives are available for infants who have not met these age thresholds, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommend using LPV/r oral solution immediately after birth in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. Ritonavir acts as a PK enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

**Efficacy**

Clinical trials involving treatment-naive adults have shown that regimens that contain LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens, including regimens that contain atazanavir, darunavir, fosamprenavir, saquinavir/ritonavir, or efavirenz. Studies have also shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that contain nelfinavir and inferior to regimens that contain darunavir.

LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and acceptable toxicity.

**Pharmacokinetics**

**General Considerations**

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 m². For the adult dose of LPV/r 400 mg/100 mg, the scaled pediatric dose would be approximately LPV/r 230 mg/57.5 mg per m² of body surface area.
However, younger children have enhanced lopinavir clearance and need higher doses to achieve lopinavir exposures similar to those seen in adults treated with standard doses. To achieve a $C_{\text{trough}}$ similar to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area. Lopinavir exposures in infants\textsuperscript{21,26,28} are compared to those in older children\textsuperscript{19} and adults\textsuperscript{29} in Table A below.

**Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age**

<table>
<thead>
<tr>
<th></th>
<th>Adults\textsuperscript{29}</th>
<th>Children\textsuperscript{19}</th>
<th>Children\textsuperscript{19}</th>
<th>Infants\textsuperscript{a} at 12 Months\textsuperscript{26}</th>
<th>Infants at 6 Weeks–6 Months\textsuperscript{21}</th>
<th>Infants at 14 Days to &lt;6 Weeks\textsuperscript{28}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV Dose</strong></td>
<td>400 mg</td>
<td>230 mg/m\textsuperscript{2}</td>
<td>300 mg/m\textsuperscript{2}</td>
<td>300 mg/m\textsuperscript{2}</td>
<td>300 mg/m\textsuperscript{2}</td>
<td>300 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td><strong>AUC\textsubscript{0-12} (mcg-hr/mL)</strong></td>
<td>92.6</td>
<td>72.6</td>
<td>116.0</td>
<td>101.0</td>
<td>74.5</td>
<td>43.4</td>
</tr>
<tr>
<td><strong>C\textsubscript{max} (mcg/mL)</strong></td>
<td>9.8</td>
<td>8.2</td>
<td>12.5</td>
<td>12.1</td>
<td>9.4</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>C\textsubscript{trough} (mcg/mL)</strong></td>
<td>7.1</td>
<td>4.7</td>
<td>7.9</td>
<td>4.9</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>C\textsubscript{min} (mcg/mL)</strong></td>
<td>5.5</td>
<td>3.4</td>
<td>6.5</td>
<td>3.8</td>
<td>2.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data were generated in a study that was cited but not reported in a final manuscript. Data in this table came from a personal communication from Edmund Capparelli, PharmD (April 18, 2012).

**Note:** Values are means; all data comes from studies where none of the participants received NNRTIs as part of their antiretroviral therapy.

**Key to Acronyms:** AUC = area under the curve; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors

Models suggest that diet, body weight, and postnatal age are important factors in lopinavir PKs, with improved bioavailability as dietary fat increases during the first year of life\textsuperscript{30} and with clearance slowing by age 2.3 years.\textsuperscript{31} A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per m\textsuperscript{2} of body surface area per dose or 300 mg per m\textsuperscript{2} of body surface area per dose in children aged 5.6 years to 12.8 years at the time of LPV/r initiation. The findings suggested that the higher dose was associated with improved long-term viral load suppression.\textsuperscript{32}

**Pharmacokinetics and Dosing**

**14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)**

The PKs of the oral solution at approximately LPV/r 300 mg/75 mg per m\textsuperscript{2} of body surface area per dose twice daily was evaluated in infants aged <6 weeks\textsuperscript{28} and infants aged 6 weeks to 6 months.\textsuperscript{21} Even at this higher dose, $C_{\text{trough}}$ levels were highly variable but were lower in infants than in children aged >6 months. $C_{\text{trough}}$ levels were lower in infants aged <6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, lopinavir area under the curve (AUC) was similar to that found in older children.\textsuperscript{26} Because infants grow rapidly in the first months of life, it is important to optimize lopinavir dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per m\textsuperscript{2} of body surface area in older children and adolescents,\textsuperscript{22} some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg per m\textsuperscript{2} of body surface area dose to allow for projected growth between clinic appointments.

**12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)**

Lower trough concentrations have been observed in children receiving LPV/r 230 mg/57.5 mg per m\textsuperscript{2} of body surface area when compared to LPV/r 300 mg/75 mg per m\textsuperscript{2} of body surface area per dose twice daily (see Table A above).\textsuperscript{18} Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m\textsuperscript{2} of body surface area per dose twice daily (when LPV/r is given without nevirapine, efavirenz, fosamprenavir, or nelfinavir), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m\textsuperscript{2} of body surface area per dose twice daily.
For infants receiving LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to “grow into” the LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily dose as they gain weight over time. Some practitioners would continue the infant dose (300 mg per m² of body surface area per dose twice daily) while using the LPV/r liquid formulation.

Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

In both children and adults, the lopinavir C\textsubscript{trough} is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant fosamprenavir or nelfinavir. Higher doses of lopinavir are recommended when the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily plus nevirapine, the mean lopinavir C\textsubscript{trough} was 3.77 ± 3.57 mcg/mL.\textsuperscript{19} Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, but the variability in concentration is much higher in children than in adults.\textsuperscript{19,33} In a study of 15 children with HIV aged 5.7 years to 16.3 years who were treated with LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in lopinavir trough concentrations. Five of 15 children (33%) had lopinavir 12-hour trough concentrations that were <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.\textsuperscript{34} A PK study in 20 children aged 10 years to 16 years who were treated with LPV/r 300 mg/75 mg per m² of body surface area twice daily plus efavirenz 350 mg per m² of body surface area once daily reported only one patient (6.6%) with subtherapeutic lopinavir trough concentrations,\textsuperscript{35} perhaps because the trial used an efavirenz dose that was approximately 11 mg/kg body weight\textsuperscript{35} instead of the 14 mg/kg body weight dose used in the trial discussed above.\textsuperscript{34}

Dosing

Once Daily

A single daily dose of LPV/r 800 mg/200 mg is approved by the FDA for treatment of HIV in treatment-naive adults aged >18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM); once-daily administration may be successful in select, closely monitored children.\textsuperscript{36} There is high interindividual variability in drug exposure for LPV/r, and trough plasma concentrations may fall below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naive children and adolescents.\textsuperscript{37-40} The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.\textsuperscript{40,41} An international, randomized, open-label trial attempted to demonstrate that once-daily LPV/r dosing was noninferior to twice-daily LPV/r dosing in children and adolescents with HIV. This trial was unsuccessful, as a greater number of children and adolescents who were on once-daily dosing had viral loads ≥50 copies/mL within 48 weeks.\textsuperscript{42}

Dosing and Its Relation to Efficacy

LPV/r is effective in treatment-experienced patients with severe immune suppression,\textsuperscript{43,44} although patients with greater prior exposure to ARV drugs may be slower to reach undetectable viral load concentrations\textsuperscript{44,45} and may have less-robust CD4 T lymphocyte (CD4) percentage responses.\textsuperscript{46}

The relationship between lopinavir exposure and the susceptibility of the HIV-1 isolate (EC\textsubscript{50}) is a key component of successful treatment. The ratio of C\textsubscript{trough} to EC\textsubscript{50} is called the inhibitory quotient (IQ), and in both adults and children treated with LPV/r, viral load reduction is more closely associated with IQ than with either C\textsubscript{trough} or EC\textsubscript{50} alone.\textsuperscript{47-49} One study investigated the use of the IQ as a guide for therapy by administering higher doses of LPV/r to children and adolescents until a target IQ of 15 was reached. This study showed that doses of LPV/r 400 mg/100 mg per m² of body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and LPV/r 480 mg/120 mg per m² of body surface area per dose twice daily (with nevirapine or efavirenz) were safe and tolerable.\textsuperscript{22} Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and suggest the potential utility of TDM when LPV/r is used in children who were previously treated with protease inhibitors.\textsuperscript{50} A lopinavir plasma concentration of ≥1 mcg/mL is cited as a minimum target trough concentration,\textsuperscript{51-53} but this...
concentration may not adequately control viremia in patients with multiple lopinavir mutations.\textsuperscript{54,55}

**Formulations**

**Palatability**

The poor palatability of the LPV/r oral solution can be a significant challenge to medication adherence for some children and families. Numbing the taste buds with ice chips before or after administering the solution, masking of the taste of the solution by administering it with sweet or tangy foods (e.g., chocolate syrup, peanut butter), or having the pharmacist flavor the solution prior to dispensing it are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.\textsuperscript{56,57}

**Do Not Use Crushed Tablets**

LPV/r tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C\textsubscript{max}, and C\textsubscript{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.\textsuperscript{58}

In a PK study using a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C\textsubscript{trough} measurements.\textsuperscript{41}

**Toxicity**

Children treated with LPV/r may have less-robust weight gain and smaller increases in CD4 percentage than children treated with NNRTI-based regimens.\textsuperscript{24,59-63} However, one study did not observe this difference in the effect of LPV/r on CD4 cell count,\textsuperscript{64} and another study found that the difference did not persist after a year of therapy.\textsuperscript{27} Some studies found no differences between the weight gain of children treated with LPV/r and those treated with efavirenz.\textsuperscript{62,65} Switching to an efavirenz-based regimen at or after age 3 years removed the risk of lopinavir-associated metabolic toxicity, with no loss of virologic control (see Table 16 in Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy).\textsuperscript{62,63} Bone mineral density improved when children were treated with efavirenz-containing regimens instead of regimens that contained LPV/r.\textsuperscript{66}

**References**


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection M-111


