Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lamivudine (3TC, Epivir)  (Last updated May 22, 2018; last reviewed May 22, 2018)

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

Formulations

Pediatric Oral Solution:
• 10 mg/mL [Epivir]
• 5 mg/mL [Epivir HBV]

Tablets:
• 150 mg (scored) and 300 mg [Epivir]
• 100 mg [Epivir HBV]

Generic Formulations:
Tablets: 100 mg, 150 mg, and 300 mg

Fixed-Dose Combination Tablets:
• [Combivir and Generic] Lamivudine 150 mg plus zidovudine 300 mg
• [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
• [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
• [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
• [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Dosing Recommendations

Note: See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12 for information about preventing perinatal transmission.

Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to <4 Weeks) Treatment Dose:
• 2 mg/kg twice daily (oral solution)

Pediatric Dose

Note: In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine is not recommended. Patients can be transitioned to once-daily treatment with the oral solution when they have been stable on twice-daily treatment for 36 weeks and are aged ≥3 years. Please see the note below and refer to the text for more detail.

Aged ≥4 Weeks to <3 Months:
• 4 mg/kg twice daily of the oral solution

Aged ≥3 Months to <3 Years:
• 5 mg/kg twice daily of the oral solution, up to 150 mg

Aged ≥3 Years:
• 5 mg/kg twice daily of the oral solution, up to

Selected Adverse Events

• Exacerbation of hepatitis has been reported after discontinuation of lamivudine in the setting of chronic hepatitis B virus (HBV) infection.

Special Instructions

• Lamivudine can be given without regard to food.
• Store lamivudine oral solution at room temperature.
• Screen patients for HBV infection before administering lamivudine.

Metabolism/Elimination

• Dose adjustment required in patients with renal insufficiency.
• Fixed-dose combination tablets should not be used in patients who are on dialysis or who have creatinine clearance <50 mL/min or impaired hepatic function.
Weight-Band Dosing (Children Weighing ≥14 kg)

Scored 150-mg Tablet

<table>
<thead>
<tr>
<th>Weight</th>
<th>Twice-Daily AM Dose</th>
<th>Twice-Daily PM Dose</th>
<th>Once-Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 kg to &lt;20 kg</td>
<td>½ tablet (75 mg)</td>
<td>½ tablet (75 mg)</td>
<td>1 tablet (150 mg)</td>
</tr>
<tr>
<td>≥20 kg to &lt;25 kg</td>
<td>½ tablet (75 mg)</td>
<td>1 tablet (150 mg)</td>
<td>1½ tablets (225 mg)</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>1 tablet (150 mg)</td>
<td>1 tablet (150 mg)</td>
<td>2 tablets (300 mg)</td>
</tr>
</tbody>
</table>

Note: The scored tablet is the preferred formulation for pediatric patients weighing ≥14 kg who can swallow a solid-dosage form.

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching children to once-daily dosing of lamivudine (oral solution or tablets) from twice-daily dosing in children aged ≥3 years, who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 T lymphocyte count. Clinicians should use a reasonable, once-daily regimen with the once-daily dose of lamivudine indicated above (approximately 10 mg/kg to a maximum of 300 mg once daily).

Child, Adolescent (Weighing ≥25 kg), and Adult Dose:

- 150 mg twice daily, or
- 300 mg once daily

[Combivir and Generic] Lamivudine plus Zidovudine

Adolescent (Weighing ≥30 kg) and Adult Dose:

- One tablet twice daily

[Trizivir and Generic] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- One tablet twice daily

[Epzicom] Abacavir plus Lamivudine

Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily
Epivir HBV oral solution and tablets contain a lower amount of lamivudine than Epivir oral solution and tablets. The amount of lamivudine in the Epivir HBV solution and tablet was based on dosing for treatment of HBV infection (in people without HIV coinfection). If Epivir HBV is used in patients with HIV, the higher dose 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 dose of lamivudine 100 mg for treatment of HIV.

**Drug Interactions** (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- Drugs that decrease renal function could decrease clearance of lamivudine.
- Do not use lamivudine in combination with emtricitabine, because these drugs have similar resistance profiles and using them together offers no additional benefit. Do not use lamivudine separately when also prescribing Truvada, Atripla, Complera, or Stribild, because emtricitabine is a component of these formulations.
- Do not use lamivudine separately when prescribing Combivir, Epzicom, Symfi Lo, or Trizivir, because lamivudine is already a component of these combinations.

**Major Toxicities**

- *Less common (more severe)*: Peripheral neuropathy, 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 and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

**Pediatric Use**

**Approval**

Lamivudine is Food and Drug Administration (FDA)-approved for the treatment of children aged ≥3 months. It is a common component of most nucleoside backbone regimens.
Considerations for Use

The efficacy and toxicity of lamivudine are equivalent to the efficacy and toxicity of emtricitabine. Formulations favor liquid emtricitabine over liquid lamivudine, since liquid emtricitabine can be given once daily at antiretroviral (ARV) initiation, but liquid lamivudine needs to be given twice daily at ARV initiation. In cases where pill formulations can be administered, lamivudine and emtricitabine are equivalent.

Comparative Clinical Trials

Studies assessing the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned with the dynamic components of the regimen (e.g., tenofovir disoproxil fumarate (TDF) or abacavir), instead of more static components like emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but little data exist to support this idea in ARV-naive patients. Investigators compared treatment-naive patients in the ATHENA cohort who started TDF/emtricitabine or TDF/lamivudine in combination with a boosted protease inhibitor (darunavir, atazanavir, or lopinavir). The adjusted hazard ratio for virologic failure of lamivudine compared to virologic failure of emtricitabine within 240 weeks of starting therapy was 1.15 (95% CI, 0.58–2.27). There was also no difference between the two groups in time to virologic suppression in the first 48 weeks of therapy or time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy that disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine are equivalent even in ARV-naive patients.

Efficacy

Lamivudine has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response. It is commonly used in children with HIV as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone. In one study, the NRTI background components of lamivudine plus abacavir were superior to zidovudine plus lamivudine or zidovudine plus abacavir in long-term virologic efficacy.

Pharmacokinetics in Infants

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. 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. For infants in early life, the higher World Health Organization weight-band dosing (which is up to five times the FDA dose) results in greater plasma concentrations than the 2 mg/kg dosing. In HPTN 040, lamivudine was given for prophylaxis of perinatal transmission during the first 2 weeks of life along with nelfinavir and 6 weeks of zidovudine according to a weight-band dosing scheme. All infants weighing >2,000 g received lamivudine 6 mg twice daily and infants weighing ≤2,000 g received lamivudine 4 mg twice daily for 2 weeks. These doses resulted in lamivudine exposure similar to that seen in infants who received the standard 2 mg/kg/dose twice-daily dosing schedule for neonates.

Pharmacokinetics of Liquid versus Tablet Preparations

The PK of lamivudine has been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved plasma concentrations of lamivudine that were approximately 25% lower than those of adults with HIV receiving oral solution. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults receiving tablets. In pediatric subjects, the relative bioavailability of lamivudine oral solution is approximately 40% lower than the relative bioavailability of tablets containing lamivudine, despite no difference in adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown, but results from a study in adults that compared the PK of lamivudine solution administered either alone or with increasing concentrations of sorbitol indicates...
that sorbitol decreases the total exposure of lamivudine solution.\textsuperscript{18} Sorbitol is a component of several ARV solutions, as well as common over-the-counter medications that may be used in infants and young children, and this may explain the PK discrepancy between the oral solution and tablet formulations. Modeling of PK data in pediatric patients suggests that increasing the lamivudine oral solution dose to 5 mg/kg/dose twice daily or 10 mg/kg/dose once daily (with a maximum of 300 mg administered daily) in children aged ≥3 months would provide exposures similar to that of adult patients receiving tablet formulations. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend once-daily dosing of lamivudine until a child is aged ≥3 years. This new dosing, however, is now reflected in the lamivudine package insert, even though there are no clinical data from patients receiving lamivudine who are also receiving sorbitol-containing medications.

Dosing Considerations—Once-Daily versus Twice-Daily Administration

The standard adult dose 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 lamivudine 8 mg/kg leads to area under the curve (AUC)\textsubscript{0-24} values that are similar to those seen in patients taking 4 mg/kg twice daily, but C\textsubscript{min} values are significantly lower and C\textsubscript{max} values are significantly higher in children aged 1 year to 18 years.\textsuperscript{19} Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in children with HIV aged 2 years to 13 years in the PENTA 13 trial,\textsuperscript{4} and in children aged 3 months to 36 months in the PENTA 15 trial.\textsuperscript{20} Both the PENTA 13 and PENTA 15 trials used a crossover design with lamivudine doses of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC\textsubscript{0-24} and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 years to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC\textsubscript{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.\textsuperscript{21} This same group conducted a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of lamivudine in more than 600 pediatric patients who initiated therapy with twice-daily lamivudine and had been receiving therapy for at least 36 weeks. Median follow-up time during the study was 114 weeks. The viral load suppression and adverse event profiles for once-daily lamivudine were noninferior to those of twice-daily lamivudine.\textsuperscript{22}

All four of the studies discussed above only enrolled patients who had a low viral load or were clinically stable on twice-daily lamivudine before switching to once-daily dosing. Nacro et al. studied a once-daily regimen composed of non-enteric-coated (EC) didanosine, lamivudine, and efavirenz. Fifty-one ARV-naive children in Burkina Faso, ranging in age from 30 months to 15 years, were enrolled in this open-label, Phase 2 study that lasted 12 months.\textsuperscript{23} The patients had advanced HIV with a mean CD4 percentage of 9% and median plasma RNA of 5.51 log\textsubscript{10} copies/mL. At the 12-month follow-up, 50% of patients had plasma RNA <50 copies/mL and 80% of patients had <300 copies/mL with marked improvements in CD4 percentage. Twenty-two percent of patients harbored multiclass-resistant viral strains. While PK values were similar to those seen during the PENTA and ARROW trials, the study was complicated by severe immunosuppression, nonclade B virus, and the use of non-EC didanosine. In addition, resistance profiles and rates of virologic failure were not separated by age. Therefore, the Panel supports switching from twice-daily to once-daily dosing of lamivudine in children aged ≥3 years who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 T lymphocyte count. Clinicians should use a 10 mg/kg/dose of lamivudine oral solution or a weight-based dose of lamivudine tablets (neither exceeding 300 mg) as part of a reasonable, once-daily regimen.\textsuperscript{24} 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 ARV therapy in children.

Lamivudine undergoes intracellular metabolism to reach 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 are equivalent to those seen in once- and twice-daily administration in adults and adolescents. This supports a recommendation for once-daily lamivudine dosing based on FDA recommendations or drug coformulations.\textsuperscript{25,26}

\textit{Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection}
World Health Organization Dosing

Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150-mg scored tablets.27,28

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, please see the Pediatric OI Guidelines.

References


