Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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**Lamivudine (3TC, Epivir)** *(Last updated September 12, 2019; last reviewed September 12, 2019)*

For additional information, see Drugs@FDA: [https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/)

### Formulations

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

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

**Generic Formulations:**
- 100 mg, 150 mg, and 300 mg tablets
- Fixed-dose combination tablet containing lamivudine 150 mg/zidovudine 300 mg

**Fixed-Dose Combination Tablets:**
- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Combivir] Lamivudine 150 mg/zidovudine 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg
- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Epzicom] Abacavir 600 mg/lamivudine 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg
- [Temixys] Lamivudine 300 mg/TDF 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also Appendix A, Table 2, Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](https://aidsinfo.nih.gov/guidelines) and [Table 12](https://www.accessdata.fda.gov/scripts/cder/daf/) for information about using lamivudine for the prevention of perinatal HIV transmission.

**Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to <4 Weeks) Dose**

**Oral Solution:**
- Lamivudine 2 mg/kg twice daily

**Infant and Child 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.

### Selected Adverse Events

- Severe exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV coinfection who discontinue lamivudine.

### 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...
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:
- Lamivudine 4 mg/kg twice daily of the oral solution

Aged ≥3 Months to <3 Years:
- Lamivudine 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)

Aged ≥3 Years:
- Lamivudine 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose); or
- 10 mg/kg once daily of the oral solution (maximum 300 mg per dose)

Weighing ≥14 kg and Able to Swallow Pills:
- Weight-band dosing (see table below; dose is approximately lamivudine 5 mg/kg/day twice daily or lamivudine 10 mg/kg once daily)

Weight-Band Dosing for the Scored, 150-mg Lamivudine Tablet in Children Weighing ≥14 kg

<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 tablet.

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

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:
- Lamivudine 150 mg twice daily; or
- Lamivudine 300 mg once daily

renal insufficiency.
- FDC tablets should not be used in patients who are on dialysis or who have creatinine clearance <50 mL/min or impaired hepatic function.
**[Cimduo] Lamivudine/TDF**  
*Child and Adolescent (Weighing ≥35 kg) and Adult Dose:*  
- One tablet once daily

**[Combivir and Generic] Lamivudine/Zidovudine**  
*Child and Adolescent (Weighing ≥30 kg) and Adult Dose:*  
- One tablet twice daily

**[Delstrigo] Doravirine/Emtricitabine/TDF**  
*Adult Dose:*  
- One tablet once daily  
- Not studied in children or adolescents (see doravirine section)

**[Dovato] Dolutegravir/Lamivudine**  
*Adult Dose:*  
- One tablet once daily with or without food as a complete antiretroviral (ARV) regimen in adults with no ARV treatment history and no known substitutions associated with resistance to the individual components of Dovato.  
- Dovato is not approved for use in children or adolescents.

**[Epzicom] Abacavir/Lamivudine**  
*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*  
- One tablet once daily

**[Symfi] Efavirenz 600 mg/Lamivudine/TDF**  
*Child and Adolescent (Weighing ≥40 kg) and Adult Dose:*  
- One tablet once daily on an empty stomach

**[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**  
*Child and Adolescent (Weighing ≥35 kg) and Adult Dose:*  
- One tablet once daily on an empty stomach

**Note:** Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1 to 3) and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 weighing ≥40 kg. Therapeutic drug monitoring is suggested by some Panel
members when Symfi Lo is used in pediatric patients weighing ≥40 kg. See the efavirenz section for more information.

**[Temixys] Lamivudine/TDF**

*Child and Adolescent (Weighing ≥35 kg) and Adult Dose:*
- One tablet once daily

**[Triumeq] Abacavir/Dolutegravir/Lamivudine**

*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*
- One tablet once daily
- This FDC tablet can be used in patients who are ARV-naive or ARV-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing >40 kg.

**[Trizivir and Generic] Abacavir/Lamivudine/ Zidovudine**

*Child and Adolescent (Weighing ≥30 kg) and Adult Dose:*
- One tablet twice daily

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4 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 co-infection. 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.

**Drug Interactions** (see also the Adult and Adolescent Antiretroviral 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.1 Do not use lamivudine with combination medications that contain lamivudine or emtricitabine. Please see Appendix A, Table 1: Antiretrovirals Available in Fixed-Dose Combination Tablets and refer to other sections of the Drug Appendix for drug interaction information about each individual component of fixed-dose combinations.

**Major Toxicities**

- **More common:** Headache, nausea.
- **Less common (more severe):** Peripheral neuropathy, lipodystrophy/lipoatrophy.
- **Rare:** Increased levels of 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 approved by the Food and Drug Administration (FDA) for the treatment of children aged ≥3 months. It is a common component of most nucleoside backbones.

Considerations for Use
The efficacy and toxicity of lamivudine are equivalent to the efficacy and toxicity of emtricitabine. Liquid emtricitabine has an advantage over liquid lamivudine, since it can be given once daily at antiretroviral (ARV) initiation while liquid lamivudine needs to be given twice daily at ARV initiation. When pill formulations of lamivudine or emtricitabine can be used, they both are administered once daily.

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, such as tenofovir disoproxil fumarate (TDF) tenofovir alafenamide (TAF), or abacavir, than the more static components, such as emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but data supporting the ability to switch between these two drugs was lacking. Investigators studying the ATHENA cohort compared the efficacy of TDF plus emtricitabine to TDF plus lamivudine when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ARV-naive patients. The adjusted hazard ratio for the virologic failure of lamivudine-containing regimens compared to emtricitabine-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). There was no difference in time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. In a Swiss cohort, Yang et al. found a potential difference in efficacy between emtricitabine and lamivudine; however, the difference disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine have equivalent efficacy and toxicity in ARV-naive patients.

Efficacy
Lamivudine has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data have demonstrated the safety of lamivudine and have shown that this drug 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 that evaluated the efficacy of NRTI background components, the combination of lamivudine plus abacavir was superior to zidovudine plus lamivudine or zidovudine plus abacavir in achieving 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 from lamivudine 2 mg/kg to lamivudine 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure. For infants, the World Health Organization weight-band dosing (which is up to five times higher than the FDA dose) results in greater plasma concentrations than the lamivudine 2 mg/kg dose. In HPTN 040, lamivudine was administered with nelfinavir and 6 weeks of zidovudine according to a weight-band dosing scheme to prevent perinatal transmission during the first 2 weeks of life. 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 lamivudine 2 mg/kg/dose twice-daily dosing schedule for neonates.
Pharmacokinetics of Liquid versus Tablet Preparations

The PKs of lamivudine have been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects who received 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 who received the oral solution. Pediatric subjects who received lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults who received tablets. In pediatric subjects, the relative bioavailability of lamivudine oral solution is approximately 40% lower than the relative bioavailability of tablets that containing lamivudine, despite no difference in the bioavailability of these two formulations among adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown, but results from a study in adults that compared the PKs of lamivudine solution administered either alone or with increasing concentrations of sorbitol indicates that sorbitol decreases the total exposure of lamivudine solution. 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; this may explain the PK discrepancy between the oral solution and tablet formulations. Modeling of PK data in pediatric patients suggests that increasing the oral solution dose to lamivudine 5 mg/kg/dose twice daily or lamivudine 10 mg/kg/dose once daily (with a maximum of lamivudine 300 mg administered daily) in children aged ≥3 months would provide exposures similar to those seen in adult patients who received 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. However, this new dosing schedule is now reflected included in the lamivudine package insert, even though there are no clinical data from patients who are receiving both lamivudine and 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)0-24 values that are similar to those seen in patients taking lamivudine 4 mg/kg twice daily, but Cmin values are significantly lower and Cmax values are significantly higher in children aged 1 year to 18 years. 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 and in children aged 3 months to 36 months in the PENTA 15 trial. Both the PENTA 13 and PENTA 15 trials used a crossover design with doses of lamivudine 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC0-24 and clearance values were similar between these two dosing schedules, and most children maintained an undetectable plasma RNA value after the switch. In the ARROW trial, a PK 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 AUC0-24h and good clinical outcome (disease stage and CD4 T lymphocyte [CD4] cell count) after a switch to once-daily lamivudine. Median follow-up time during this study was 1.15 years. ARROW is a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of lamivudine in >600 pediatric patients who had initiated therapy with twice-daily lamivudine and who had been receiving therapy for ≥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.

All four of the studies discussed above only enrolled patients who had a low viral load or who 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. The patients had advanced HIV with a mean CD4 percentage of 9% and a median plasma RNA of 5.51 log10 copies/mL. At the 12-month follow-up visit, 50% of patients had plasma RNA <50 copies/mL and 80% of patients had <300 copies/mL and 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 the presence of severe immunosuppression and 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 cell count. Clinicians should use a 10 mg/kg/dose of lamivudine oral solution or a weight-based dose of lamivudine tablets (neither exceeding lamivudine 300 mg) as part of a reasonable, once-daily regimen. 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 whether given once-daily or twice-daily in adults and adolescents. This supports a recommendation for once-daily lamivudine dosing based on FDA recommendations.

World Health Organization Dosing

Weight-band dosing recommendations for lamivudine have been developed for children weighing ≥14 kg and receiving the 150-mg scored tablets.

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, and other topics related to opportunistic infections, please see the Pediatric Opportunistic Infections Guidelines.

References


