



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lamivudine (3TC, Epivir) (Last updated April 27, 2017; last reviewed April 27, 2017)

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^a)

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

Fixed-Dose Combination Tablets:

- [Combivir and generic] Lamivudine 150 mg plus zidovudine 300 mg
- [Epzicom] Abacavir 600 mg plus lamivudine 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

Generic Formulations

Tablets: 100 mg, 150 mg, and 300 mg

Dosing Recommendations

Neonate and Infant Dose (Birth to <4 Weeks):

- 2 mg/kg twice daily

Note: Please see [Infant ARV Prophylaxis in 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 dosing used to prevent perinatal transmission.

Pediatric Dose (Aged ≥4 Weeks):

- 4 mg/kg (up to 150 mg) twice daily
- In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine is not generally recommended. Please refer to text for more detail.

Weight-Band Dosing (Weighing ≥14 kg)

Scored 150 mg tablet

Weight	Twice-Daily AM Dose	Twice-Daily PM Dose	Once-Daily Dose
14 to <20 kg	½ tablet (75 mg)	½ tablet (75 mg)	1 tablet 150 mg
≥20 to <25 kg	½ tablet (75 mg)	1 tablet (150 mg)	1½ tablets 225 mg
≥25 kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets (300 mg)

Selected Adverse Events

- Minimal toxicity
- 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

- Renal excretion: Dosage adjustment required in renal insufficiency.
- Fixed-dose combination tablets should not be used in patients with creatinine clearance <50 mL/min, on dialysis, or with impaired hepatic function.

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged ≥ 3 years with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 T lymphocyte count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily.

Adolescent and Adult Dose:

Weighing <25 kg:

- 4 mg/kg (up to 150 mg) twice daily

Weighing ≥ 25 kg:

- 150 mg twice daily or 300 mg once daily

[Combivir and Generic] Lamivudine/Zidovudine

Adolescent (Weighing ≥ 30 kg)/Adult Dose:

- 1 tablet twice daily

[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

Adolescent (Weighing ≥ 40 kg)/Adult Dose:

- 1 tablet twice daily

[Epzicom] Abacavir/Lamivudine

Adolescent (Weighing ≥ 25 kg)/Adult Dose:

- 1 tablet once daily

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Adolescent (Weighing ≥ 40 kg)/Adult Dose:

- 1 tablet once daily

^a Epivir HBV oral solution and tablets contain a lower amount of lamivudine than Epivir oral solution and tablets. The strength of lamivudine in 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 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 lamivudine dose for treatment of HIV.

Drug Interactions (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors:* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit.¹ Do not use separately when prescribing Truvada, Atripla, Complera, or Stribild because emtricitabine is a component of these formulations. Do not use separately when prescribing Combivir, Epzicom, or Trizivir because lamivudine is already a component of these combinations.

Major Toxicities

- *More common:* Headache, nausea.
- *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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

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 emtricitabine. Formulations favor liquid emtricitabine over liquid lamivudine, since liquid emtricitabine can be given once daily at ARV initiation but liquid lamivudine needs to be given twice daily at ARV initiation. When pill formulations can be administered, again, 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 or abacavir versus the more static components [e.g. emtricitabine or lamivudine]). Emtricitabine and lamivudine have been considered interchangeable, but little data exists to make this recommendation in ARV-naïve patients. Investigators in the ATHENA cohort compared naïve patients who started tenofovir/emtricitabine or tenofovir/lamivudine in combination with a boosted protease inhibitor (darunavir, atazanavir, or lopinavir).² The adjusted hazard ratio for virologic failure of lamivudine compared to emtricitabine within 240 weeks of starting therapy was 1.15 (95% CI, 0.58–2.27). There was also no difference in time to virologic suppression in the first 48 weeks of therapy or the time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy which disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine are equivalent even in ARV-naïve patients.³

Efficacy

Lamivudine has been studied in children with HIV alone and in combination with other ARV drugs. Extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response, and it is commonly used in children with HIV as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone.⁴⁻¹² In 1 study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.¹³

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.⁹ 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.¹⁴ For infants in early life, the higher World Health Organization weight-band dosing (up to 5 times the FDA dose) results in increased plasma concentrations compared to the 2 mg/kg dosing.¹⁵ In HPTN 040, lamivudine was given for prophylaxis of perinatal transmission in 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 6 mg twice daily and infants weighing $\leq 2,000$ g received 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.¹⁶

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 approximately 25% lower plasma concentrations of lamivudine compared with 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. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown,¹⁷ but a recent study in adults comparing the PK of lamivudine solution either alone or with increasing concentrations of sorbitol indicates that sorbitol decreases the total exposure of lamivudine solution.¹⁸ Sorbitol is a component of several ARV solutions used in pediatric patients, and this may explain the PK discrepancy between oral solution and tablet formulations. There are currently no studies supporting an increase in dosing for lamivudine oral solution in children.

Dosing Considerations—Once-Daily versus Twice-Daily Administration

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.¹⁹ Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in children with HIV aged 2 to 13 years in the PENTA-13 trial,⁴ and in children aged 3 to 36 months in the PENTA 15 trial.²⁰ Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC₀₋₂₄ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC₀₋₂₄ 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.²¹ All 3 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-naïve children in Burkina-Faso composed of non-enteric-coated (EC) didanosine, 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.²² The patients had advanced HIV with a mean CD4 percentage of 9 and median plasma RNA of 5.51 log₁₀/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-EC didanosine, 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 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 ARV therapy in children.

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 based upon FDA recommendations or drug co-formulations.^{23,24}

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.^{25,26}

Both emtricitabine and lamivudine have antiviral activity and efficacy against HBV. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, please see the [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children](#).

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