



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lamivudine (3TC, Epivir) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

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 (Aged <4 Weeks) for Treatment:

- 2 mg/kg twice daily

Note: Please see [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 (Weight ≥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)	1 ½ 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 infection.

Special Instructions

- Lamivudine can be given without regard to food.
- Store lamivudine oral solution at room temperature.
- Screen patients for Hepatitis B virus 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.

Adolescent and Adult Dose:

Body Weight <25 kg:

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

Body Weight ≥25 kg:

- 150 mg twice daily or 300 mg once daily

[Combivir and Generic] Lamivudine plus Zidovudine

Adolescent (Weighing ≥30 kg) and Adult Dose:

- 1 tablet twice daily

[Trizivir and Generic] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet twice daily.

[Epzicom] Abacavir plus Lamivudine

Adolescent (Weighing ≥25 kg) and Adult Dose:

- 1 tablet once daily

[Triumeq] Abacavir plus Dolutegravir plus Lamivudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet once daily

The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (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.

^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 hepatitis B virus (HBV) infection (in people without HIV coinfection). If Epivir HBV is used in HIV-infected patients, 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 infection.

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 treatment of children aged ≥ 3 months, and it is a common component of most nucleoside backbone regimens.

Efficacy

Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral (ARV) drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response, and it is commonly used in HIV-infected children as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone.²⁻¹⁰ In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.¹¹

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.⁷ 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.¹² 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.¹³ 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.¹⁴

Pharmacokinetics of Liquid Versus Tablet Preparations

The PK of lamivudine have 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 HIV-1-infected adults 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.¹⁵ There are currently no studies supporting an increase in dosing for lamivudine oral solution in children. Care should be taken if considering once-daily dosing with the liquid preparation.

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.¹⁶ Intensive PKs of

once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children aged 2 to 13 years in the PENTA-13 trial,² and in children aged 3 to 36 months in the PENTA 15 trial.¹⁷ 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.¹⁸ All three 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.¹⁹ The patients had advanced HIV infection 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-enteric-coated 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 year 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.**^{20,21}

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.^{22,23}

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 [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children](#).

References

1. Anderson PL, Lamba J, Aquilante CL, Schuetz E, Fletcher CV. Pharmacogenetic characteristics of indinavir, zidovudine, and lamivudine therapy in HIV-infected adults: a pilot study. *J Acquir Immune Defic Syndr*. 2006;42(4):441-449. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16791115>.
2. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther*. 2005;10(2):239-246. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15865218>.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793-800. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16148846>.
4. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J*. 2005;24(12):1072-1076.

Available at <http://www.ncbi.nlm.nih.gov/pubmed/16371868>.

5. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
6. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J*. 2006;25(6):533-537. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16732152>.
7. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr*. 2005;39(2):189-194. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15905735>.
8. Mueller BU, Lewis LL, Yuen GJ, et al. Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. 1998;42(12):3187-3192. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9835513>.
9. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. 2000;283(4):492-498. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10659875>.
10. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kujipers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. 2006;117(3):e528-536. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16481448>.
11. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS*. 2007;21(8):947-955. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17457088>.
12. Tremoulet AH, Capparelli EV, Patel P, et al. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother*. 2007;51(12):4297-4302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17893155>.
13. Tremoulet AH, Nikanjam M, Cressey TR, et al. Developmental pharmacokinetic changes of Lamivudine in infants and children. *J Clin Pharmacol*. 2012;52(12):1824-1832. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22180560>.
14. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nelfinavir and Lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J*. 2011;30(9):769-772. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21666540>.
15. Choi SY, Li F, Florian J, Seo SK. Lamivudine and abacavir clinical summary review. 2014. Available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446104.pdf>. Accessed February 17, 2016.
16. Bouazza N, Hirt D, Blanche S, et al. Developmental pharmacokinetics of lamivudine in 580 pediatric patients ranging from neonates to adolescents. *Antimicrob Agents Chemother*. 2011;55(7):3498-3504. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21576443>.
17. Paediatric European Network for Treatment of Aids. Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-36 months. *Antivir Ther*. 2010;15(3):297-305. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20516550>.
18. Musiime V, Kendall L, Bakeera-Kitaka S, et al. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther*. 2010;15(8):1115-1124. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21149918>.
19. Nacro B, Zoure E, Hien H, et al. Pharmacology and immuno-virologic efficacy of once-a-day HAART in African HIV-infected children: ANRS 12103 phase II trial. *Bull World Health Organ*. 2011;89(6):451-458. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21673861>.
20. Yuen GJ, Lou Y, Bumgarner NF, et al. Equivalent steady-state pharmacokinetics of lamivudine in plasma and lamivudine triphosphate within cells following administration of lamivudine at 300 milligrams once daily and 150 milligrams twice daily. *Antimicrob Agents Chemother*. 2004;48(1):176-182. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14693537>.
21. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother*. 2007;51(10):3516-3522. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/17664328>.

22. World Health Organization. Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: Report of the WHO paediatric antiretroviral working group. 2008. Available at http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf. Accessed February 17, 2016.
23. L'Homme R F, Kabamba D, Ewings FM, et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS*. 2008;22(5):557-565. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18316996>.