Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lamivudine (3TC/Epivir) (Last updated November 1, 2012; last reviewed November 1, 2012)

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

Formulations

Oral solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBVa)

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

Combination tablets:

- *With zidovudine (ZDV):* 150 mg 3TC + 300 mg ZDV (generic and Combivir)
- *With abacavir (ABC):* 300 mg 3TC + 600 mg ABC (Epzicom)
- *With ZDV and ABC:* 150 mg 3TC + 300 mg ZDV + 300 mg ABC (Trizivir)

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The strength of 3TC in Epivir HBV solution and tablet was maximized for treatment of hepatitis B virus (HBV) only. 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 3TC dose for treatment of HIV infection.

Dosing Recommendations

Neonate/infant dose (age <4 weeks) for prevention of transmission or treatment:

- 2 mg/kg twice daily.

Pediatric dose (age ≥4 weeks):

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

Pediatric dosing for scored 150-mg tablet (weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21–<30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (age ≥16 years)/adult dose:

- *Body weight ≥50 kg:*
  150 mg twice daily or 300 mg once daily.
- *Body weight <50 kg:*
  4 mg/kg (up to 150 mg) twice daily.

Selected Adverse Events

- Minimal toxicity
- Exacerbation of hepatitis has been reported after discontinuation of 3TC in the setting of chronic hepatitis B infection.

Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before administering 3TC.

Metabolism

- Renal excretion—dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function

Combivir

- *Adolescent (weight ≥30 kg)/adult dose:*
  1 tablet twice daily.

Trizivir

- *Adolescent (weight >40 kg)/adult dose:*
  1 tablet twice daily.

Epzicom

- *Adolescent (age >16 years and weight >50 kg)/adult dose:*
  1 tablet once daily.

Drug Interactions: (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit.[1]

Major Toxicities:

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, pancreatitis, 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/3TC.html).

Pediatric Use: Lamivudine is Food and Drug Administration (FDA)-approved for use in children aged ≥3 months, and it is a common component of most nucleoside backbone regimens.

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.[2-17] Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone.[3, 4, 6, 7, 11, 12, 14, 16, 17] In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.[18] Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150 mg scored tablets.[19, 20]

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.[11] 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.[21] For infants in the first 2 weeks of life, weight-band dosing has also been used. In HPTN 040, all infants weighing >2000 g received 6 mg twice daily and infants weighing ≤2000 g received 4 mg twice daily for 2 weeks. These doses resulted in similar lamivudine exposure as in infants

receiving the standard 2 mg/kg/dose twice daily dosing schedule for neonates.[22]

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 $(AUC)_{0\text{-}24}$ 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.[23] Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in HIV-infected children ages 2 to 13 years in the PENTA-13 trial[2] and in children 3 to 36 months of age in the PENTA 15 trial.[24] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. $AUC_{0\text{-}24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children ages 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent $AUC_{0\text{-}24}$ 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.[25] 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-naive children in Burkina-Faso composed of non-enteric-coated didanosine (ddI), 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.[26] The patients had advanced HIV infection with a mean CD4 percentage of 9 and a median plasma RNA of 5.51 $\log_{10}$/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 ddI, 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 and older 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 antiretroviral therapy in children.

Steady-State Pharmacokinetics of Once- or Twice-Daily Lamivudine

Study/(reference)	PENTA 15[24]		PENTA 13[2]		ARROW[25]	
	Europe		Europe		Uganda	
N	17		14		35	
	2		5		7	
Sex (% male)	56%		43%		42%	
	78%		Not Reported		100%	
	11		19		19	
Concurrent PI use	8		1		0	
Dosing interval (hours)	12	24	12	24	12	24
Administered dose (mg/kg)	4.04	8.02	4.05	8.1	4.7	9.6
$AUC_{0\text{-}24}$ (mg*hr/L)	9.48[a]	8.66[a]	8.88[a]	9.80[a]	11.97[a]	12.99[a]
C_{max} (mg/L)	1.05[a]	1.87[a]	1.11[a]	2.09[a]	1.80[a]	3.17[a]
C_{min} (mg/L)	0.08[a]	0.05[a]	0.067[a]	0.056[a]	0.08[a]	0.05[a]
Cl/F/kg (L/hr/kg)	0.79[a]	0.86[a]	0.90[a]	0.80[a]	0.79[a]	0.72[a]

Data are medians except as noted.

[a] Geometric mean

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 in adolescents aged 16 and older who weigh 50 kg or more.[27, 28]

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