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

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Lamivudine (Epivir, 3TC)
(Last updated November 14, 2017; last reviewed November 14, 2017)

Available evidence does not suggest that lamivudine use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes.

Animal Studies
Carcinogenicity
Lamivudine has weak mutagenic activity in one in vitro assay but no evidence of in vivo genotoxicity in rats at 35 to 45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.1

Reproduction/Fertility
Lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the offspring’s survival, growth, and development up to the time of weaning.1

Teratogenicity/Adverse Pregnancy Outcomes
There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryo lethality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.1

Placental and Breast Milk Passage
In studies of pregnant rats, lamivudine is transferred to the fetus through the placenta.1

Human Studies in Pregnancy
Pharmacokinetics
Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in 2 separate studies.2,3 This was confirmed in a larger analysis of 114 pregnant women, 123 women in labor, and 47 non-pregnant women, in which all received standard once- or twice-daily lamivudine doses.4 Pregnant women had a 22% higher apparent clearance than non-pregnant and postpartum women, but this increase did not lead to subtherapeutic exposure. The level of lamivudine exposure in pregnant women, although lower than exposure in non-pregnant and parturient women, was relatively close to data reported previously for non-pregnant adults.4 Thus, no dose adjustment in pregnancy is necessary.

Placental and Breast Milk Passage
Lamivudine readily crosses the placenta in humans, achieving cord blood levels comparable to maternal concentrations.3 In a study of 123 mother/infant pairs, the placental transfer expressed as fetal-to-maternal area under the curve (AUC) ratio was 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.4 Other studies have also noted accumulation of lamivudine in amniotic fluid due to urinary excretion of lamivudine by the fetus into amniotic fluid.2

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56.5 In infants who were exposed to lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (IC50 of lamivudine against wild-type HIV = 0.6–21 ng/mL). In a separate study of breastfeeding women in Malawi who were receiving lamivudine (in combination with tenofovir and efavirenz), concentrations of lamivudine in breast milk were higher than those in maternal plasma at 1 month (3.29-fold higher) and 12 months (2.35-fold higher) after delivery; infant plasma levels at ages 6 and 12 months, on the other hand, revealed median (IQR) lamivudine concentrations of only 2.5 (2.5-7.6) and 0 (0-2.5) ng/mL, respectively.6
Teratogenicity/Adverse Pregnancy Outcomes

In a large French cohort, lamivudine exposure in the first trimester was associated with an increased risk of overall birth defects (adjusted odds ratio = 1.37; 95% CI, 1.06–1.73) but there was no organ system or specific birth defect that predominated. However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in cardiovascular and genitourinary defects (the most common classes). No such increase in birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (145 of 4,763 births; 95% CI, 2.6% to 3.6%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.

An analysis of Antiretroviral Pregnancy Registry data demonstrated lower risk of spontaneous abortions, induced abortions, and preterm births for lamivudine-containing regimens compared with non-lamivudine antiretroviral regimens.

Other Safety Information

In a large, U.S. cohort study of uninfected infants born to women living with HIV, lamivudine exposure during pregnancy was not associated with increased risk of adverse infant outcomes in any of the growth, hearing, language, neurology, neurodevelopment, metabolic, hematologic/clinical chemistry, and blood lactate domains assessed.

Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (3TC) Epivir (3TC/ZDV) Combivir (3TC/ABC) Epzicom (3TC/ZDV/ABC) Trizivir (3TC/ABC/DTG) Triumeq</td>
<td>3TC (Epivir) Tablets: • 150 mg• 300 mg Oral Solution: • 10 mg/mL Combivir: • 3TC 150 mg plus ZDV 300 mg tablet Epzicom: • 3TC 300 mg plus ABC 600 mg tablet Trizivir: • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet Triumeq: • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet</td>
<td>Standard Adult Dose 3TC (Epivir): • 150 mg twice daily or 300 mg once daily, without regard to food Combivir: • 1 tablet twice daily without regard to food Epzicom: • 1 tablet once daily without regard to food Trizivir: • 1 tablet twice daily without regard to food Triumeq: • 1 tablet once daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.</td>
<td>High placental transfer to fetus. No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If HBV-coinfected, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection.</td>
</tr>
</tbody>
</table>

— Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7).
— Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:
  High: >0.6 Moderate: 0.3–0.6 Low: <0.3
— Generic formulation available

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; HBV = hepatitis B virus; PK = pharmacokinetic; ZDV = zidovudine

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References


