



**Recommendations for the Use of Antiretroviral Drugs in
Pregnant Women with HIV Infection and Interventions to Reduce
Perinatal HIV Transmission in the United States**

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Lamivudine (Epivir, 3TC)

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Available evidence suggests that lamivudine use by pregnant women is not 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 there was no evidence of *in vivo* genotoxicity in rats at 35 times to 45 times the exposure in humans receiving standard dosing. Long-term animal studies have shown no evidence of carcinogenicity at 10 times and 58 times human exposure in mice and rats, respectively.¹

Reproduction/Fertility

Lamivudine administered to rats at doses up to 4000 mg/kg/day, which produced plasma levels 47 times to 70 times those seen in humans who received standard dosing, revealed no evidence of impaired fertility and no effects 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 exposures that were similar to human therapeutic exposure, but no early embryo lethality was seen in rats with lamivudine exposures that were 35 times the human exposure level.¹

Placental and Breast Milk Passage

In studies of pregnant rats, lamivudine was transferred to the fetus through the placenta.¹

Human Studies in Pregnancy

Pharmacokinetics

Two separate studies have reported that pregnancy does not significantly affect lamivudine pharmacokinetic parameters.^{2,3} This was confirmed in an analysis of 114 pregnant women, 123 women in labor, and 47 nonpregnant women, in which all participants received standard once-daily or twice-daily lamivudine doses.⁴ Pregnant women had a 22% higher apparent clearance than nonpregnant 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 nonpregnant and parturient women, was relatively close to results reported previously for nonpregnant adults.⁴ Thus, no dose adjustment for lamivudine is necessary during pregnancy.

Placental and Breast Milk Passage

Lamivudine readily crosses the placenta in humans, achieving cord blood levels comparable to maternal plasma 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 who received 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, the 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 disoproxil fumarate 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 lamivudine concentrations of only 2.5 ng/mL (with an interquartile range [IQR] of 2.5–7.6) and 0 ng/mL (with an IQR of 0–2.5), 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 affected organ system or specific birth defect that predominated.⁷ However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a two-fold increase in the risk of cardiovascular and genitourinary defects (the most common classes of birth defects in the general population). No such increase in the risk of 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% (151 of 5,008 births; 95% CI, 2.6% to 3.5%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

An analysis of Antiretroviral Pregnancy Registry data demonstrated a lower risk of spontaneous abortions, induced abortions, and preterm births with use of lamivudine-containing regimens compared with use of non-lamivudine antiretroviral regimens.⁹

Other Safety Information

In a large U.S. cohort study of infants without HIV 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.¹⁰

Excerpt from Table 10^a

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of the individual drug components of the FDC during pregnancy.

| Generic Name (Abbreviation) Trade Name | Formulation | Dosing Recommendations | Use in Pregnancy |
|---|---|---|--|
| Lamivudine (3TC) <i>EpiVir</i> (3TC/TDF) <i>Cimduo</i> (3TC/ZDV) <i>Combivir</i> (3TC/DOR/TDF) <i>Delstrigo</i> (3TC/ABC) <i>Epzicom</i> (3TC/EFV/TDF) <i>Symfi</i> (3TC/EFV/TDF) <i>Symfi Lo</i> (3TC/TDF) <i>Temixys</i> (3TC/ABC/DTG) <i>Triumeq</i> (3TC/ABC/ZDV) <i>Trizivir</i> Note: Generic available for some formulations | 3TC (EpiVir) ^d <i>Tablets:</i> • 150 mg • 300 mg <i>Oral Solution:</i> • 10 mg/mL | <u>Standard Adult Doses</u> 3TC (EpiVir): • 3TC 150 mg twice daily or 300 mg once daily, without regard to food 3TC/TDF (Cimduo): • 1 tablet once daily without regard to food 3TC/ZDV (Combivir): • 1 tablet twice daily without regard to food 3TC/DOR/TDF (Delstrigo): • 1 tablet once daily without regard to food 3TC/ABC (Epzicom): • 1 tablet once daily without regard to food 3TC/EFV/TDF (Symfi or Symfi Lo): • 1 tablet once daily on an empty stomach and preferably at bedtime 3TC/ABC/DTG (Triumeq): • 1 tablet once daily without regard to food 3TC/TDF (Temixys): • 1 tablet once daily without regard to food 3TC/ABC/ZDV (Trizivir): • 1 tablet twice daily without regard to food | High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). If patient has HIV/ HBV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see HIV/Hepatitis B Virus Coinfection . Note: 3TC products developed specifically for treatment of HBV (e.g., EpiVir-HBV) contain a lower dose of 3TC that is not appropriate for treatment of HIV. |
| | 3TC/TDF (Temixys): • 3TC 300 mg plus ABC 600 mg tablet | PK in Pregnancy: • PK not significantly altered in pregnancy. | |
| | 3TC/ABC/DTG (Triumeq): • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg tablet | <u>Dosing in Pregnancy:</u> • No change in dose indicated. | |
| | 3TC/ABC/ZDV (Trizivir): ^d • 3TC 150 mg plus ABC 300 mg plus ZDV 300 mg tablet | For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, DOR, DTG, EFV, TDF, ZDV). | |

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

^d Generic formulation available

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; **DOR = doravirine**; DTG = dolutegravir; **EFV = efavirenz**; HBV = hepatitis B virus; PK = pharmacokinetic; **TDF = tenofovir disoproxil fumarate**; ZDV = zidovudine

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