



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)

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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.†

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.†

Teratogenicity/Developmental Toxicity

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.†

Human Studies in Pregnancy

Pharmacokinetics

Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in two 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 sub-therapeutic 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 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1214 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).

Teratogenicity/Developmental Toxicity

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% confidence interval [CI], 1.06–1.73) but there was no organ system or specific birth defect that predominated.⁶ However, in the Antiretroviral Pregnancy Registry (APR), 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 APR, the prevalence of birth defects was 3.1% (143 of 4,566 births; 95% CI, 2.6% to 3.7%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁷

Other Pregnancy Outcomes

An analysis of APR data demonstrated lower risk of spontaneous abortions, induced abortions, and preterm births for lamivudine-containing regimens compared with non-lamivudine antiretroviral regimens.⁸

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Lamivudine (3TC) <i>Epivir</i> (3TC/ZDV) <i>Combivir</i> (3TC/ABC) <i>Epzicom</i> (3TC/ZDV/ABC) <i>Trizivir</i> (3TC/ABC/DTG) <i>Triumeq</i>	<u>3TC (Epivir)</u> <u>Tablets:</u> <ul style="list-style-type: none"> • 150 mg • 300 mg <u>Oral Solution:</u> <ul style="list-style-type: none"> • 10 mg/mL <u>Combivir:</u> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg tablet <u>Epzicom:</u> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg tablet <u>Trizivir:</u> <ul style="list-style-type: none"> • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet <u>Triumeq:</u> <ul style="list-style-type: none"> • 3TC 300 mg plus ABC 600 mg plus DTG 50-mg tablet 	<u>Standard Adult Dose(s)</u> <u>3TC (Lamivudine):</u> <ul style="list-style-type: none"> • 150 mg twice daily or 300 mg once daily, without regard to food <u>Combivir:</u> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <u>Epzicom:</u> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <u>Trizivir:</u> <ul style="list-style-type: none"> • 1 tablet twice daily without regard to food <u>Triumeq:</u> <ul style="list-style-type: none"> • 1 tablet once daily without regard to food <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> • No change in dose indicated. 	High placental transfer to fetus. ^b 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 .

^a Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, Appendix B, Table 7](#)).

^b Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

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

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