Lamivudine (Epivir, 3TC)

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Animal Studies

Carcinogenicity

Lamivudine (3TC) was found to have weak mutagenic activity in one *in vitro* assay, but no evidence of *in vivo* genotoxicity was found in rats at 35 to 45 times the exposure observed in humans who received the standard dose. Long-term animal studies have shown no evidence of carcinogenicity at exposures that were 10 times (in mice) and 58 times (in rats) the exposure seen in humans who received the standard dose.[1]

Reproduction/Fertility

In rats that received 3TC in doses up to 4,000 mg/kg per day, which produced plasma levels 47 to 70 times those seen in humans who received the standard dose, no evidence was found of impaired fertility and no effects on the offspring's survival, growth, or development up to the time of weaning.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence exists of 3TC-induced teratogenicity in rats and rabbits at plasma concentrations of 3TC that are 35 times those seen in human plasma. 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 3TC exposures that were 35 times the exposure observed in humans who received the standard dose.[1]

Placental and Breast Milk Passage

In studies of pregnant rats, 3TC was transferred to the fetus through the placenta.[1]

Human Studies in Pregnancy

Pharmacokinetics

In an analysis of specimens obtained from 228 pregnant women in the antepartum (114), intrapartum (123) and postpartum (47) periods in which all participants received standard once-daily or twice-daily 3TC doses,[2] women had a 22% higher apparent clearance rate during pregnancy than in the postpartum period, but the resulting lower 3TC exposure in pregnant women was not subtherapeutic and was relatively close to exposure reported previously for nonpregnant adults.[2] Thus, no dose adjustment is necessary for 3TC during pregnancy.

Placental and Breast Milk Passage

3TC readily crosses the placenta in humans, achieving cord blood concentrations comparable to maternal plasma concentrations.[3] In a study of 123 mother–infant pairs, the placental transfer, expressed as the fetal-to-maternal area under the curve (AUC) ratio, was 0.86. The 3TC amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.[2] Urinary excretion of 3TC by the fetus can cause 3TC to accumulate in the amniotic fluid.[4]

3TC is excreted into human breast milk. In a study in Kenya of 67 nursing mothers who received a combination regimen of zidovudine, 3TC, and nevirapine, the median breast milk 3TC concentration was 1,214 ng/mL and the median ratio of 3TC concentration in breast milk to the concentration in plasma was 2.56.[5] In infants who were exposed to 3TC only via breast milk, the median plasma 3TC concentration was 23 ng/mL (inhibitory concentration 50% [IC_{50}] of 3TC against wild-type HIV = 0.6–21 ng/mL). In a separate study of breastfeeding women in Malawi who were receiving 3TC in combination with tenofovir disoproxil fumarate and efavirenz, concentrations of 3TC 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 3TC 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] Lower 3TC exposure in these older infants is attributable to increased renal clearance with age.

Teratogenicity/Adverse Pregnancy Outcomes

Based on prospective reports to the Antiretroviral Pregnancy Registry (APR), the FDA has concluded that no difference exists between the overall risk of birth defects for lamivudine compared with the background birth defect rate in the United States.[1]

In a large French cohort, 3TC exposure during 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 not of a defect in any specific organ system or of a specific birth defect.[7] However, the Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to 3TC to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with 3TC. Among the cases of first-trimester 3TC exposure that have been reported to the APR, the prevalence of birth defects was 3.1% (167 of 5,353 live births; 95% CI, 2.7% to 3.6%) 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 than with use of antiretroviral regimens that do not include lamivudine.[9]

Other Safety Information

In a large U.S. cohort study of infants without HIV born to women with HIV, 3TC 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

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

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Lamivudine (3TC) *Epivir* (3TC/TDF) *Cimduo* (3TC/ZDV) *Combivir* (3TC/DOR/TDF) *Delstrigo* (3TC/DTG) *Dovato* (3TC/ABC) *Epzicom* (3TC/EFV/TDF) *Symfi* (3TC/EFV/TDF) *Symfi Lo* (3TC/TDF) *Temixys* (3TC/ABC/DTG) *Triumeq* (3TC/ABC/ZDV) *Trizivir* **Note:** Generic products are available for some formulations.	**3TC (Epivir)**[d] *Tablets:* • 150 mg • 300 mg *Oral Solution:* • 10 mg/mL **3TC/TDF (Cimduo):** • 3TC 300 mg/TDF 300 mg tablet **3TC/ZDV (Combivir):**[d] • 3TC 150 mg/ZDV 300 mg tablet **3TC/DOR/TDF (Delstrigo):** • 3TC 300 mg/DOR 100 mg/TDF 300 mg tablet **3TC/DTG (Dovato):** • 3TC 300 mg/DTG 50 mg tablet **3TC/ABC (Epzicom):**[d] • 3TC 300 mg/ABC 600 mg tablet **3TC/EFV/TDF (Symfi):** • 3TC 300 mg/EFV 600 mg plus TDF 300 mg tablet **3TC/EFV/TDF (Symfi Lo):** • 3TC 300 mg/EFV 400 mg/TDF 300 mg tablet	**Standard Adult Doses** *3TC (Epivir):* • 3TC 150 mg twice daily or 300 mg once daily, without regard to food *3TC/TDF (Cimduo):* • One tablet once daily without regard to food *3TC/ZDV (Combivir):* • One tablet twice daily without regard to food *3TC/DOR/TDF (Delstrigo):* • One tablet once daily without regard to food *3TC/DTG (Dovato):* • One tablet once daily without regard to food *3TC/ABC (Epzicom):* • One tablet once daily without regard to food *3TC/EFV/TDF (Symfi or Symfi Lo):* • One tablet once daily on an empty stomach and preferably at bedtime *3TC/TDF (Temixys):* • One tablet once daily without regard to food *3TC/ABC/DTG (Triumeq):* • One tablet once 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 HBV/HIV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection. 3TC products that were developed specifically for treatment of HBV (e.g., Epivir-HBV) contain a lower dose of 3TC that **is not appropriate** for treatment of HIV.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	3TC/TDF (Temixys): • 3TC 300 mg/TDF 300 mg tablet **3TC/ABC/DTG (Triumeq):** • 3TC 300 mg/ABC 600 mg/DTG 50 mg tablet **3TC/ABC/ZDV (Trizivir):**[d] • 3TC 150 mg/ABC 300 mg/ZDV 300 mg tablet	*3TC/ABC/ZDV (Trizivir):* • One tablet twice daily without regard to food **Pregnancy** *PKs in Pregnancy:* • PKs not significantly altered in pregnancy. *Dosing in Pregnancy:* • No change in dose indicated. For guidance about the 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 doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[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 product available

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; HBV = hepatitis B virus; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

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