



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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Stavudine (Zerit, d4T)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Stavudine is classified as Food and Drug Administration (FDA) Pregnancy Category C.

Animal Studies

Carcinogenicity

Stavudine is clastogenic in *in vitro* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year carcinogenicity studies in mice and rats, stavudine was non-carcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.¹

Reproduction/Fertility

Stavudine has not been shown to have an effect on reproduction or fertility in rodents. No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.¹ A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100 μ M and of post-blastocyst development at 10 μ M.²

Teratogenicity/Developmental Toxicity

No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, that seen at a clinical dosage of 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—was increased at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times human exposure, with no effect noted at approximately 135 times human exposure. An increase in early rat neonatal mortality (birth to day 4) occurred at 399 times human exposure, although survival of neonates was unaffected at approximately 135 times the human exposure.¹

Placental and Breast Milk Passage

A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.¹

In primates (pig-tailed macaques), fetal/maternal plasma concentrations were approximately 0.80.³ Stavudine is excreted into the breast milk of lactating rats.¹

Human Studies in Pregnancy

Pharmacokinetics

In a Phase I/II safety and pharmacokinetic (PK) study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332), both drugs were well tolerated, with stavudine PK parameters similar to those in non-pregnant adults.⁴

Placental and Breast Milk Passage

Stavudine crosses the human placenta, resulting in a **cord/maternal blood** concentration of **1.0–1.3**.⁵ Stavudine also crosses into human breast milk, resulting in breast milk/maternal plasma concentrations of 1.0 to 1.76. Concentrations in nursing infants were negligible.^{6,7}

Teratogenicity/Developmental Toxicity

No association was found between first-trimester exposure to stavudine and birth defects in a large French

cohort study that had 70% power to detect an increased adjusted odds ratio of 1.5.⁸ In the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a two-fold increased risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the APR, the prevalence of birth defects was 2.6% (21 of 810 births; 95% CI, 1.6% to 3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.⁹

Other Safety Data

Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents.¹⁰⁻¹² The FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination (see [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) and [Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants](#)). These drugs should not be prescribed together for pregnant women.

Excerpt from Table 8^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Stavudine (d4T) Zerit	<u>d4T (Zerit)</u> Capsules: • 15 mg • 20 mg • 30 mg • 40 mg Oral Solution: • 1 mg/mL following reconstitution	<u>Standard Adult Dose(s)^d</u> <i>Body Weight ≥60 kg:</i> • 40 mg twice daily without regard to meals <i>Body Weight <60 kg:</i> • 30 mg twice daily without regard to meals <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy. <u>Dosing in Pregnancy:</u> • No change in dose indicated.	High placental transfer. ^b No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). d4T should not be used with ddl or ZDV. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together.

^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

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: d4T = stavudine; ddl = didanosine; PK = pharmacokinetic; WHO = World Health Organization; ZDV = zidovudine

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