Stavudine (Zerit, d4T)

(Last updated December 7, 2018; last reviewed December 7, 2018)

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

Stavudine **is not recommended** for use in pregnant women with HIV due to its toxicity.

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 noncarcinogenic at doses that produced exposures 39 times (in mice) and 168 times (in rats) the human exposure observed at the recommended therapeutic dose. At higher levels of exposure (250 times [in mice] and 732 times [in rats] the human exposure seen 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 no demonstrated 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 the exposures observed following a clinical dosage of stavudine 1 mg/kg/day.[1] A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation occurring at a concentration of 100 μM and inhibition of post-blastocyst development occurring at 10 μM.[2]

Teratogenicity/Adverse Pregnancy Outcomes

No evidence of teratogenicity was noted in rats or rabbits with stavudine exposures (based on C_{max}) up to 399 times and 183 times, respectively, the exposures seen at a clinical dosage of stavudine 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—increased at 399 times human exposure (i.e., the exposure in adult humans who received a standard dose), 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 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), the ratio of fetal plasma concentrations/maternal plasma concentrations was approximately 0.80.[3]

Stavudine is excreted into the breast milk of lactating rats.[1]

Human Studies in Pregnancy

Pharmacokinetics

In a Phase 1/2 short-term safety and pharmacokinetic (PK) study of combination stavudine and lamivudine in pregnant women living with HIV and their infants (PACTG 332), both drugs were well tolerated, with maternal stavudine PK parameters similar to those seen in nonpregnant adults.[4]

Placental and Breast Milk Passage

Stavudine crosses the human placenta, resulting in cord blood concentration/maternal blood concentration ratios of 1.0 to 1.3.[5] Stavudine also crosses into human breast milk, resulting in breast milk concentration/maternal plasma concentration ratios of 1.0 to 1.76. Concentrations in nursing infants were negligible.[6,7]

Teratogenicity/Adverse Pregnancy Outcomes

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, 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 Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.6% (21 of 811 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

Cases of lactic acidosis, including some fatal cases, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral (ARV) agents.[10-12] The FDA and Bristol-Myers Squibb 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 Infants Exposed to Antiretroviral Drugs). Didanosine and stavudine **should not be prescribed together** for pregnant women.

In a U.S. cohort study evaluation of the safety of ARV drugs used during pregnancy, children without HIV born to women with HIV who received didanosine plus stavudine during the pregnancy had an increased risk of both adverse neurodevelopmental (relative risk [RR] of 12.40; 95% CI, 5.29–29.08) and language (RR of 4.84, 95% CI, 1.14–20.51) outcomes compared to children whose mothers did not receive these drugs during pregnancy.[13]

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Excerpt from Table 10[a]

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**	**Use in Pregnancy**
Stavudine (d4T) *Zerit* **Note:** Generic products are available for all formulations.	d4T (Zerit) *Capsules:* • 15 mg • 20 mg • 30 mg • 40 mg *Oral Solution:* • 1 mg/mL following reconstitution **Note:** Extended-release capsule formulation (Zerit XR) has been discontinued by the manufacturer.	Standard Adult Doses[e] *Body Weight ≥60 kg:* • 40 mg twice daily without regard to meals *Body Weight <60 kg:* • 30 mg twice daily without regard to meals Dosing in Pregnancy: • No change in dose indicated. PK in Pregnancy: • PK not significantly altered in pregnancy.	d4T **is not recommended** for pregnant women. High placental transfer.[b] No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects). Lactic acidosis, sometimes fatal, has been reported in pregn aant women receiving ddI and d4T together.

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

[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

[e] WHO recommends maximum dose of 30 mg twice daily regardless of weight.

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; PK = pharmacokinetic; WHO = World Health Organization

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