



**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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## ***Didanosine (Videx, ddI)***

**(Last updated April 29, 2016; last reviewed April 29, 2016)**

Didanosine is classified as Food and Drug Administration (FDA) Pregnancy Category B.<sup>1</sup>

### **Animal Studies**

#### *Carcinogenicity Studies*

Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies of 0.7 to 1.7 times human exposure in mice and 3 times human exposure in rats have been negative.<sup>1</sup>

#### *Reproduction/Fertility*

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.

#### *Teratogenicity/Developmental Toxicity*

No evidence of teratogenicity or toxicity was observed with administration of didanosine at 12 and 14 times human exposure, respectively, in pregnant rats and rabbits.

#### *Placental and Breast Milk Passage*

A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta.

### **Human Studies in Pregnancy**

#### *Pharmacokinetics*

A Phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.<sup>2</sup> The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic (PK) parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

#### *Placental and Breast Milk Passage*

Placental transfer of didanosine was low-moderate in a Phase I/II safety and PK study.<sup>2</sup> This was confirmed in a study of 100 HIV-infected pregnant women who were receiving nucleoside reverse transcriptase inhibitors (NRTIs) (generally as part of a two- or three-drug combination antiretroviral [ARV] regimen). At the time of delivery, cord-to-maternal-blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection.<sup>3</sup>

It is not known if didanosine is excreted in human breast milk.

#### *Teratogenicity*

The French Perinatal Cohort reported an association of head and neck birth defects with first-trimester exposure to didanosine (0.5%, AOR = 3.4 (95% Confidence Interval [CI] 1.1–10.4), *P* = 0.04).<sup>4</sup> The PHACS/SMARTT cohort found no association between any NRTIs and birth defects.<sup>5</sup> Among 897 births to HIV-infected women in a Spanish cohort, there was no significant difference in the rate of birth defects between first-trimester compared to the second- and third-trimester exposure (OR 0.61, 95% CI, 0.16, 2.27).<sup>6</sup> Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.7% (20 of 423 births; 95% CI, 2.9% to 7.2%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>7</sup> All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

#### *Safety*

Lactic acidosis, fatal in some cases, has been described in pregnant women receiving the combination of

didanosine and stavudine along with other ARV agents;<sup>8-10</sup> 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.

### Excerpt from Table 8<sup>a</sup>

Generic Name (Abbreviation) Trade Name.	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Didanosine</b> (ddl) Videx Videx EC	<u>ddl (Videx)</u> <u>Buffered Tablets (Non-EC):</u> • No longer available  <u>Solution:</u> • 10 mg/mL oral solution  <u>Videx EC (EC Beadlets) Capsules:</u> • 125 mg • 200 mg • 250 mg • 400 mg  <u>Generic Delayed-Release Capsules:</u> • 200 mg • 250 mg • 400 mg	<u>Standard Adult Doses</u> <u>Body Weight ≥60 kg:</u> • 400 mg once daily  <u>With TDF:</u> • 250 mg once daily; take 1/2 hour before or 2 hours after a meal.  <u>Body Weight &lt;60kg:</u> • 250 mg once daily  <u>With TDF:</u> • 200 mg once daily; take 1/2 hour before or 2 hours after a meal.  <b>Note:</b> Preferred dosing with oral solution is twice daily (total daily dose divided into 2 doses); take 1/2 hour before or 2 hours after a meal.  <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	Low-moderate placental transfer to fetus. <sup>b</sup>  In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddl compared to general population was noted after both first-trimester (20/423, 4.7%; 95% CI, 2.9% to 7.2%) and later exposure (20/461, 4.3%; 95% CI 2.7% to 6.6%). No specific pattern of defects was noted and clinical relevance is uncertain.  ddl <b>should not be used</b> with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Appendix B, Table 7](#)).

<sup>b</sup> 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:** APR = Antiretroviral Pregnancy Registry; CI = confidence interval; d4T = stavudine; ddl = didanosine; EC = enteric coated; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

## References

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