



**Recommendations for the Use of Antiretroviral Drugs in  
Pregnant Women with HIV Infection and Interventions to Reduce  
Perinatal HIV Transmission in the United States**

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## ***Didanosine (Videx, ddl)***

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

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

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

### **Animal Studies**

#### *Carcinogenicity*

Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies of 0.7 times 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/Adverse Pregnancy Outcomes*

No evidence of teratogenicity or toxicity was observed in pregnant rats and rabbits with exposures of didanosine that were 12 times and 14 times, respectively, the exposures seen in humans.

#### *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 1 study (PACTG 249) of didanosine was conducted in 14 pregnant women with HIV who were 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 1/2 safety and PK study.<sup>2</sup> This was confirmed in a study of 100 pregnant women with HIV 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). In 15 of 24 samples (62%), cord blood concentrations for didanosine were below the limits of detection.<sup>3</sup>

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

#### *Teratogenicity/Adverse Pregnancy Outcomes*

The French Perinatal Cohort reported that head and neck birth defects were associated with first-trimester exposure to didanosine (0.5%, adjusted odds ratio [aOR] 3.4, 95% CI, 1.1–10.4,  $P = 0.04$ ).<sup>4</sup> Though the PHACS/SMARTT cohort found no association between any individual NRTIs and birth defects, after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with an overall increase in congenital abnormalities;<sup>5</sup> it should be noted that the combination of didanosine and stavudine **should not be used** in pregnant women with HIV (or anyone with HIV) because of a higher risk of toxicity. Among 897 births to women with HIV in a Spanish cohort, there was no significant difference between the rate of birth defects after first-trimester exposure and the rate of birth defects after second- and third-trimester exposure (odds ratio [OR] 0.61, 95% CI, 0.16–2.27).<sup>6</sup> In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to didanosine in humans have been monitored to be able to detect at least a 2-fold increase in

the risk of overall birth defects.<sup>7</sup> Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was **4.68%** (20 of **427** births; 95% CI, **2.88%** to **7.14%**) compared with 2.72% 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.

The PHACS/SMARTT cohort found that after adjusting for birth cohort and other factors, didanosine administered in combination with stavudine was associated with the occurrence of neurodevelopmental disability. However, there was no increase in the likelihood of adverse events in the following domains with didanosine alone: metabolic, growth and development, cardiac, neurological, neurodevelopmental, behavior, language, and hearing.<sup>11,12</sup> As noted above, the combination of didanosine and stavudine should not be used in pregnant women with HIV (or anyone with HIV) because of a high risk of toxicity.

In a multivariate analysis of the association between *in utero* ARV exposure and risk of cancer in HIV-exposed, uninfected infants, the French Perinatal Study reported a 5.5-fold (95% CI, 2.1–14.4) increase in cancer incidence with first-trimester didanosine exposure.<sup>13</sup>

### Excerpt from Table 10<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Didanosine (ddl) Videx Videx EC	<u>ddl (Videx)</u> Buffered Tablets (Non-EC): • No longer available  Solution: • 10 mg/mL oral solution  <u>Videx EC (EC Beadlets)</u> <u>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> • ddl 400 mg once daily  <u>With TDF:</u> • ddl 250 mg once daily; take 1/2 hour before or 2 hours after a meal.  <u>Body Weight &lt;60 kg:</u> • ddl 250 mg once daily  <u>With TDF:</u> • ddl 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>Dosing in Pregnancy:</u> • No change in dose indicated.  <u>PK in Pregnancy:</u> • PK is not significantly altered in pregnancy.	ddl <b>is not recommended</b> for pregnant women.  Low-moderate placental transfer to fetus. <sup>b</sup>  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 ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Guidelines, Appendix B, Table 8](#)).

<sup>b</sup> 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

**Key to Acronyms:** ARV = antiretroviral; d4T = stavudine; ddl = didanosine; EC = enteric coated; FDC = fixed-dose combination; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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