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 November 14, 2017; last reviewed November 14, 2017)*

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

**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.1

**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.

**Adverse Pregnancy Outcomes**

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 pregnant women with HIV enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.2 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.2 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) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection.3

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

**Adverse Pregnancy Outcomes**

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% CI, 1.1–10.4), P = 0.04).4 Though the PHACS/SMARTT cohort found no association between any individual NRTIs and birth defects, after adjusting for birth cohort and other factors, didanosine in combination with stavudine was associated with an overall increase in congenital abnormalities;5 it should be noted that the combination of didanosine and stavudine should no longer be used in pregnant women with HIV (or anyone with HIV) because of higher risk of toxicity. Among 897 births to women with HIV 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).6 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.4 Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.74% (20 of 422 births; 95% CI, 2.91% to 7.23%) compared with
2.73% in the U.S. population, based on Centers for Disease Control and Prevention surveillance. 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; 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 in combination with stavudine was associated with 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. As noted above, the combination of didanosine and stavudine should no longer be used in pregnant women with HIV (or anyone with HIV) because of higher risk of toxicity.

In a multivariate analysis of the association of 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.

Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name.</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine (ddI) Videx Videx EC</td>
<td>ddl (Videx) Buffered Tablets (Non-EC):</td>
<td>Standard Adult Doses Body Weight ≥60 kg:</td>
<td>Low-moderate placental transfer to fetus.</td>
</tr>
<tr>
<td></td>
<td>• No longer available Solution:</td>
<td>• 400 mg once daily</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• 10 mg/mL oral solution</td>
<td>With TDF:</td>
<td>ddl should not be used with d4T. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddl and d4T together.</td>
</tr>
<tr>
<td></td>
<td>Videx EC (EC Beadlets) Capsules:</td>
<td>• 250 mg once daily; take 1/2 hour before or 2 hours after a meal.</td>
<td>Note: 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.</td>
</tr>
<tr>
<td></td>
<td>• 125 mg</td>
<td>Body Weight &lt;60 kg:</td>
<td>PK in Pregnancy:</td>
</tr>
<tr>
<td></td>
<td>• 200 mg</td>
<td>• 250 mg once daily</td>
<td>• PK not significantly altered in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• 250 mg</td>
<td>With TDF:</td>
<td>Dosing in Pregnancy:</td>
</tr>
<tr>
<td></td>
<td>• 400 mg</td>
<td>• 200 mg once daily; take 1/2 hour before or 2 hours after a meal.</td>
<td>• No change in dose indicated.</td>
</tr>
</tbody>
</table>

* Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7).

* Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

<table>
<thead>
<tr>
<th>High:</th>
<th>Moderate:</th>
<th>Low:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.6</td>
<td>0.3–0.6</td>
<td>&lt;0.3</td>
</tr>
</tbody>
</table>

Key to Acronyms: APR = Antiretroviral Pregnancy Registry; CI = confidence interval; d4T = stavudine; ddl = didanosine; EC = enteric coated; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate
References


