



**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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## Glossary of Terms for Supplement

**Carcinogenic** = producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

**Clastogenic** = causing disruption of or breakages in chromosomes

**Genotoxic** = damaging to genetic material such as DNA and chromosomes

**Mutagenic** = inducing or capable of inducing genetic mutation

**Teratogenic** = interfering with fetal development and resulting in birth defects

## Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Data are available from clinical trials in human pregnancy for the nucleoside NRTIs zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir disoproxil fumarate (tenofovir). The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. Tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base and, hence, requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see [Recommendations for Use of Antiretroviral Drugs During Pregnancy and Long-Term Follow-Up of Antiretroviral Drug-Exposed Infant](#).

### *Abacavir (Ziagen, ABC)*

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Abacavir is classified as Food and Drug Administration Pregnancy Category C.

#### **Animal Studies**

##### *Carcinogenicity*

Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.

##### *Reproduction/Fertility*

No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).

##### *Teratogenicity/Developmental Toxicity*

Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (increased resorptions and decreased fetal body weight) occurred with administration of 500 mg/kg/day of abacavir to pregnant rodents. The offspring of female rats were treated with 500 mg/kg of abacavir, beginning at embryo implantation and ending at weaning. In these animals, an increased incidence of stillbirth and lower body weight was seen throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

##### *Placental and Breast Milk Passage*

Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.<sup>1</sup>

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## Human Studies in Pregnancy

### Pharmacokinetics

A Phase I study of abacavir in pregnant women indicates that the AUC drug concentration during pregnancy was similar to that at 6 to 12 weeks postpartum and in non-pregnant individuals.<sup>2</sup> Thus, no dose adjustment for abacavir is needed during pregnancy.

### Placental and Breast Milk Passage

In the Mma Bana study,<sup>1</sup> at 1 month postpartum, the median breast milk-to-plasma ratio for abacavir was 0.85 in the 15 women tested, and the drug was detected in the plasma of 1 of 9 breastfeeding infants whose mothers were receiving abacavir.

### Teratogenicity

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. Among cases of first-trimester abacavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (27 of 905 births; 95% CI, 2.0% to 4.3%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>3</sup> There was no association of birth defects with first trimester exposure to abacavir in the SMARTT study (aOR 0.94 [0.53–1.65])<sup>4</sup> or in the French Perinatal Study (aOR 1.01, [0.73–1.41]).<sup>5</sup>

### Safety

Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults, but these reactions have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Patients who test positive for HLA-B\*5701 are at highest risk; HLA screening should be done before initiation of abacavir.

### Excerpt from Table 7<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Abacavir</b> (ABC) Ziagen	<u>ABC (Ziagen)</u> <i>Tablet:</i> • 300 mg  <i>Solution:</i> • 20 mg/mL	<u>Standard Adult Doses</u> <i>ABC (Ziagen):</i> • 300 mg twice daily or 600 mg once daily, without regard to food  <i>Epzicom:</i> • 1 tablet once daily without regard to food  <i>Trizivir:</i> • 1 tablet twice daily without regard to food	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).  Hypersensitivity reactions occur in approximately 5% to 8% of non-pregnant individuals; a much smaller percentage are fatal and are usually associated with re-challenge. Rate in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.
(3TC/ABC) Epzicom	<u>Epzicom:</u> • ABC 600 mg plus 3TC 300 mg tablet	<u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.	
(ZDV/3TC/ABC) Trizivir	<u>Trizivir:</u> • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet	<u>Dosing in Pregnancy:</u> • No change in dose indicated.	
(DTG/ABC/3TC) Triumeq	<u>Triumeq:</u> • Dolutegravir 50 mg plus ABC 600 mg plus 3TC 300 mg		

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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 Abbreviations:** 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; PK = pharmacokinetic; ZDV = zidovudine

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

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

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

### **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.

#### *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>1</sup> The drug was well tolerated during pregnancy by the women and the fetuses. 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 pharmacokinetic (PK) study.<sup>1</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>2</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% CI 1.1–10.4), *P* = 0.04).<sup>3</sup> The PHACS/SMARTT cohort found no association between any NRTIs and birth defects.<sup>3,4</sup> Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 4.8% (20 of 418 births; 95% CI, 2.9% to 7.3%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>5</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>6–8</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. These two drugs should be prescribed together to

pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

**Excerpt from Table 7<sup>a</sup>**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Didanosine</b> (ddl) <i>Videx</i> <i>Videx EC</i>	<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 APR, an increased rate of birth defects with ddl compared to general population was noted after both first-trimester (20/413, 4.8%; 95% CI, 3.0% to 7.4%) and later exposure (20/460, 4.3%; 95% CI 2.7% to 6.6%). No specific pattern of defects was noted and clinical relevance is uncertain. ddl should not be used 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 [Adult Guidelines, 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 Abbreviations:** APR = Antiretroviral Pregnancy Registry; CI = confidence interval; d4T = stavudine; ddl = didanosine; EC = enteric coated; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

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## ***Emtricitabine (Emtriva, FTC)***

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Emtricitabine is classified as Food and Drug Administration Pregnancy Category B.

### **Animal Studies**

#### *Carcinogenicity*

Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term carcinogenicity studies of oral emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 26 times the human systemic exposure or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.<sup>1</sup>

#### *Reproduction/Fertility*

No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by area under the curve [AUC]) approximately 60-fold higher in female and male mice and 140-fold higher in male rats than human exposure at the recommended therapeutic dose.<sup>1</sup>

#### *Teratogenicity/Developmental Toxicity*

Incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice that resulted in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.<sup>1</sup>

#### *Placental and Breast Milk Passage*

Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits.<sup>2</sup>

### **Human Studies in Pregnancy**

#### ***Pharmacokinetics***

Emtricitabine pharmacokinetic (PK) parameters have been evaluated in 18 HIV-infected pregnant women receiving antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum.<sup>3</sup> Emtricitabine exposure was modestly lower during the third trimester (8.6 mcg\*h/mL [5.2–15.9]) compared with the postpartum period (9.8 mcg\*h/mL [7.4–30.3]). Two-thirds (12 of 18) of pregnant women versus 100% (14 of 14) of postpartum women met the AUC target (10th percentile in non-pregnant adults). Trough emtricitabine levels were also lower during pregnancy (minimum plasma concentration 52 ng/mL [14–180]) compared with the postpartum period (86 ng/mL [<10 to 306]). In the IMPAACT P1026s study, 26 women had emtricitabine PKs assessed during the third trimester (median 35 weeks) and 22 postpartum (mean 8 weeks postpartum).<sup>4</sup> The PK parameters during pregnancy were slightly altered in comparison to PK parameters during the postpartum period, with higher emtricitabine clearance (25.0 vs. 20.6 L/hour during pregnancy vs. postpartum, respectively) and lower 24-hour post-dose levels (0.058 vs. 0.085 mg/L), but the 24-hour, post-dose levels were well above the inhibitory concentration 50% (IC<sub>50</sub>) in all patients. Similar differences in PK parameters of emtricitabine among women during pregnancy or after delivery were found in the PACTG 394 study<sup>5</sup> and in a European study.<sup>6</sup> **A population PK study of 83 pregnant women and 103 non-pregnant control women demonstrated that the 18% increase in emtricitabine clearance in pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.<sup>7</sup>** Thus, these changes are not believed to be large enough to warrant dosage adjustment during pregnancy.

#### *Placental and Breast Milk Passage*

Emtricitabine has been shown to have excellent placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine once daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and the mean ratio of cord blood/maternal emtricitabine concentrations was 1.17 ± 0.6 (n = 9).<sup>3</sup> In a

study of 15 women enrolled in IMPAACT P1026s who received emtricitabine during pregnancy, the mean cord-to-maternal-blood ratio was 1.2 (90% confidence interval [CI], 1.0–1.5).<sup>4</sup> In 8 women enrolled in PACTG 394 who were given a single dose of 600 mg emtricitabine with 900 mg tenofovir disoproxil fumarate, the median cord blood emtricitabine concentration was 717 ng/mL (range 21–1,072), and the median cord blood/maternal ratio was 0.85 (range 0.46–1.07).<sup>5</sup>

Emtricitabine is excreted into human milk. In a study in the Ivory Coast, 5 HIV-infected women who chose to exclusively breastfeed their newborn infants were given 400 mg emtricitabine, 600 mg tenofovir, and 200 mg nevirapine at onset of labor, followed by 200 mg emtricitabine and 300 mg tenofovir once daily for 7 days postpartum. The median minimal and maximal concentrations of emtricitabine in breast milk were 177 and 679 ng/mL, respectively (interquartile ranges 105–254 and 658–743 ng/mL, respectively), well above the estimated emtricitabine IC<sub>50</sub> for HIV-1.<sup>8</sup>

#### *Teratogenicity/Developmental Toxicity*

In a study of pregnancies occurring during an HIV pre-exposure prophylaxis (PrEP) trial in which HIV-uninfected participants were randomized to placebo, tenofovir, or tenofovir plus emtricitabine, there was no increase in congenital anomalies in the tenofovir-plus-emtricitabine arm.<sup>9</sup> There was no overall difference in the rate of pregnancy loss in the tenofovir-plus-emtricitabine or tenofovir-alone arms of this PrEP study. In a large French cohort, emtricitabine exposure in the first trimester was associated with lower risk of birth defects.<sup>10</sup> In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects. No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (35 of 1,543 births; 95% CI, 1.6% to 3.1%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>11</sup>

Excerpt from Table 7<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Emtricitabine</b> (FTC) <i>Emtriva</i>	<u>FTC (Emtriva)</u> <i>Capsules:</i> • 200 mg  <i>Oral Solution:</i> • 10 mg/mL	<u>Standard Adult Dose(s)</u> <i>FTC (Emtriva)</i> <u>Capsule:</u> • 200 mg once daily without regard to food  <u>Oral Solution:</u> • 240 mg (24 mL) once daily without regard to food	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects).  If HBV-coinfected, it is possible that a hepatitis B flare may occur if the drug is stopped postpartum; see <a href="#">HIV/Hepatitis B Virus Coinfection</a> .
(FTC/TDF) <i>Truvada</i>	<u>Truvada:</u> • FTC 200 mg plus TDF 300 mg tablet	<i>Truvada:</i> • 1 tablet once daily without regard to food	
(FTC/TDF/EFV) <i>Atripla</i>	<u>Atripla:</u> • FTC 200 mg plus TDF 300 mg plus EFV <sup>c</sup> 600 mg tablet	<i>Atripla:</i> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.	
(FTC/TDF/RPV) <i>Complera</i>	<u>Complera:</u> • FTC 200 mg plus TDF 300 mg plus RPV 25 mg tablet	<i>Complera:</i> • 1 tablet once daily with food	
(FTC/TDF/EVG/ COBI) <i>Stribild</i>	<u>Stribild:</u> • FTC 200 mg plus TDF 300 mg plus EVG 150 mg plus COBI 150 mg tablet	<i>Complera:</i> • 1 tablet once daily with food  <i>Stribild:</i> • 1 tablet once daily with food  <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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 Abbreviations:** COBI = cobicistat; EFV = efavirenz; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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## ***Lamivudine (Epivir, 3TC)***

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Lamivudine is classified as Food and Drug Administration Pregnancy Category C.

### **Animal Studies**

#### *Carcinogenicity*

Lamivudine has weak mutagenic activity in one *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35 to 45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.<sup>1</sup>

#### *Reproduction/Fertility*

Lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the offspring's survival, growth, and development up to the time of weaning.<sup>1</sup>

#### *Teratogenicity/Developmental Toxicity*

There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits.

Early embryoletality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.<sup>1</sup>

### **Human Studies in Pregnancy**

#### ***Pharmacokinetics***

Pregnancy does not significantly affect lamivudine pharmacokinetic parameters, as reported in two separate studies.<sup>2,3</sup> This was confirmed in a larger analysis of 114 pregnant women, 123 women in labor, and 47 non-pregnant women, in which all received standard once- or twice-daily lamivudine doses.<sup>4</sup> Pregnant women had a 22% higher apparent clearance than non-pregnant and postpartum women, but this increase did not lead to sub-therapeutic exposure. The level of lamivudine exposure in pregnant women, although lower than exposure in non-pregnant and parturient women, was relatively close to data reported previously for non-pregnant adults.<sup>4</sup> Thus, no dose adjustment in pregnancy is necessary.

#### *Placental and Breast Milk Passage*

Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations.<sup>3</sup> In a study of 123 mother/infant pairs, the placental transfer expressed as fetal-to-maternal area under the curve (AUC) ratio was 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.<sup>4</sup> Other studies have also noted accumulation of lamivudine in amniotic fluid due to urinary excretion of lamivudine by the fetus into amniotic fluid.<sup>2</sup>

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56.<sup>5</sup> In infants who were exposed to lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (IC<sub>50</sub> of lamivudine against wild-type HIV = 0.6–21 ng/mL).

#### *Teratogenicity/Developmental Toxicity*

In a large French cohort, lamivudine exposure in the first trimester was associated with an increased risk of overall birth defects (adjusted odds ratio = 1.37, 95% CI 1.06-1.73) but there was no organ system or specific birth defect that predominated.<sup>6</sup> However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects, such as defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed

with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (137 of 4,418 births; 95% CI, 2.6% to 3.7%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>7</sup>

**Excerpt from Table 7<sup>a</sup>**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Lamivudine</b> (3TC) <i>Epivir</i>	<u>3TC (Epivir)</u> <i>Tablets:</i> • 150 mg • 300 mg  <i>Oral Solution:</i> • 10 mg/mL	<u>Standard Adult Dose(s)</u> <i>3TC (Lamivudine):</i> • 150 mg twice daily or 300 mg once daily, without regard to food  <i>Combivir:</i> • 1 tablet twice daily without regard to food	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).  If HBV-coinfected, it is possible that an HBV flare may occur if the drug is stopped; see <a href="#">HIV/Hepatitis B Virus Coinfection</a> .
(3TC/ZDV) <i>Combivir</i>	<u>Combivir:</u> • 3TC 150 mg plus ZDV 300 mg tablet	<i>Epzicom:</i> • 1 tablet once daily without regard to food	
(3TC/ABC) <i>Epzicom</i>	<u>Epzicom:</u> • 3TC 300 mg plus ABC 600 mg tablet	<i>Trizivir:</i> • 1 tablet twice daily without regard to food	
(3TC/ZDV/ABC) <i>Trizivir</i>	<u>Trizivir:</u> • 3TC 150 mg plus ZDV 300 mg plus ABC 300 mg tablet	<u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.	
(3TC/ABC/DTG) <i>Triumeq</i>	<u>Triumeq:</u> • 3TC 300 mg plus ABC 600 mg plus DTG 50 mg	<u>Dosing in Pregnancy:</u> • No change in dose indicated.	

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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 Abbreviations:** 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; HBV = hepatitis B virus; PK = pharmacokinetic; ZDV = zidovudine

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## **Stavudine (Zerit, d4T)**

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

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.

#### *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.**<sup>1</sup> A dose-related cytotoxic effect has been observed on pre-implantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100  $\mu$ M and of post-blastocyst development at 10  $\mu$ M.<sup>2</sup>

#### *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.

#### *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.

In primates (pig-tailed macaques), fetal/maternal plasma concentrations were approximately 0.80.<sup>3</sup> Stavudine is excreted into the breast milk of lactating rats.

### **Human Studies in Pregnancy**

#### **Pharmacokinetics**

A Phase I/II safety and pharmacokinetic (PK) study has been conducted of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332). Both drugs were well tolerated, with stavudine PKs similar to those in non-pregnant adults.<sup>4</sup>

#### *Placental and Breast Milk Passage*

Stavudine crosses the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. 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.<sup>5,6</sup>

#### *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.**<sup>7</sup> 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 809 births; 95% CI, 1.6% to 4.0%) compared with a total prevalence in the US population of 2.7%, based on Centers for Disease Control and Prevention surveillance.<sup>8</sup>

#### 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 (ARV) agents.<sup>9-11</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 (see [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) and [Long-Term Follow-Up of Antiretroviral Drug-Exposed Infant](#)). These drugs should be prescribed together for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

#### Excerpt from Table 7<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Stavudine</b> (d4T) Zerit	d4T (Zerit) Capsules: • 15 mg • 20 mg • 30 mg • 40 mg Oral Solution: • 1 mg/mL following reconstitution	<u>Standard Adult Dose(s)</u> <i>Body Weight ≥60 kg:</i> • 40 mg twice daily without regard to meals <i>Body Weight &lt;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. <sup>b</sup> 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.

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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 Abbreviations:** d4T = stavudine; ddl = didanosine; PK = pharmacokinetic; ZDV = zidovudine

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## **Tenofovir Disoproxil Fumarate (Viread, TDF)**

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Tenofovir disoproxil fumarate, **the orally bioavailable form of tenofovir**, is classified as Food and Drug Administration Pregnancy Category B.

### **Animal Studies**

#### *Carcinogenicity*

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

#### *Reproduction/Fertility*

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose, respectively, based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats for 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day.

#### *Teratogenicity/Developmental Toxicity*

Chronic exposure of fetal monkeys to tenofovir at high doses (exposure equivalent to 25 times the area under the curve (AUC) achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment.

#### *Placental and Breast Milk Passage*

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir crosses the placenta.<sup>1</sup>

### **Human Studies in Pregnancy**

#### **Pharmacokinetics**

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 non-pregnant women receiving combination regimens including tenofovir, pregnant women had a 39% higher apparent clearance of tenofovir compared with non-pregnant women, which decreased slightly but significantly with increasing age.<sup>2</sup> In a P1026s study of 19 pregnant women receiving tenofovir-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum, the percentage of women with tenofovir AUC exceeding the target of 2 µg\*hour/mL (the 10th percentile in non-pregnant adults) was lower in the third trimester (74%, 14 of 19 women) than postpartum (86%, 12 of 14 women) ( $P = 0.02$ ); however, trough levels were similar in the two groups.<sup>3</sup> In another study of 34 women receiving tenofovir plus emtricitabine in the third trimester and postpartum, **tenofovir AUC, peak, and trough were all about 25% lower in pregnant women compared to postpartum women, but these decreased exposures** were not associated with virologic failure.<sup>4</sup> Standard dosing during pregnancy continues to be recommended.

#### *Placental and Breast Milk Passage*

In studies of pregnant women on chronic tenofovir, the cord-to-maternal-blood ratio ranged from 0.60 to 1.03, indicating high placental transfer.<sup>3-6</sup> In studies of pregnant women receiving single-dose tenofovir (with

and without emtricitabine) in labor, the drugs were well tolerated and the median tenofovir cord-to-maternal-blood ratio at delivery ranged from 0.55 to 0.73.<sup>7,8</sup> Intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of 600 mg tenofovir with 400 mg emtricitabine, but intracellular tenofovir diphosphate was detectable in only 2 (5.5%) of 36 infants.<sup>9</sup>

Sixteen breast milk samples were obtained from five women who received 600 mg tenofovir at the start of labor followed by 300 mg daily for 7 days. Tenofovir levels in breast milk ranged from 5.8 to 16.3 ng/mL, resulting in nursing infants ingesting an estimated daily amount of tenofovir that corresponds to 0.03% of the proposed oral dose of tenofovir for neonates.<sup>10</sup> Because the form of tenofovir in breastmilk is expected to have lower bioavailability than tenofovir, these exposures are likely overestimates. No studies have measured tenofovir blood levels in infants breastfed by women taking tenofovir.

### *Reproduction/Fertility*

A retrospective analysis of 7,275 women (1,199 receiving tenofovir-based combination antiretroviral therapy) demonstrated a slight reduction in pregnancy rates, but the findings were limited by the observational nature of the data and additional studies are needed for confirmation.<sup>11</sup>

### *Teratogenicity/Developmental Toxicity*

In a study of 431 pregnancies occurring during an HIV pre-exposure prophylaxis trial in which HIV-uninfected women were randomized to placebo, tenofovir, or tenofovir plus emtricitabine, there was no difference in risk of congenital anomalies between the tenofovir-containing and placebo arms.<sup>12</sup> No association was seen between maternal tenofovir and offspring birth defects in three large U.S. cohorts: PACT 219/219C (n = 2,202 with 214 first-trimester tenofovir exposures), P1025 (n = 1,112 with 138 first-trimester tenofovir exposures),<sup>13,14</sup> and Pediatric HIV AIDS Cohort Study (n = 2,580 with 431 first-trimester tenofovir exposures).<sup>15</sup> In the French Perinatal Cohort, no association was found between birth defects and tenofovir with a power of 70% for an odds ratio of 1.5 (n = 13,124 with 823 first-trimester tenofovir exposures).<sup>16</sup> Finally, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to tenofovir in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects. No increase in birth defects has been observed with tenofovir. Among cases of first-trimester tenofovir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (47 of 2,141 births; 95% confidence interval [CI], 1.6% to 2.9%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>17</sup>

### *Other Safety Data*

Among 382 pregnancies occurring in 302 women in Uganda and Zimbabwe participating in the DART trial—approximately two-thirds of whom received tenofovir through more than 90% of their pregnancies—there were no differences noted in mortality, birth defects, or growth.<sup>18</sup> In the Pediatric HIV/AIDS Cohort Study from the United States, 449 (21%) of the 2,029 HIV-exposed but uninfected infants had *in utero* exposure to tenofovir, and there was no difference at birth between those exposed to combination drug regimens with or without tenofovir in low birthweight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively). However, at age 1 year, infants exposed to combination regimens with tenofovir had a slight but significantly lower adjusted mean LAZ and HCAZ than those without tenofovir exposure (LAZ: -0.17 vs. -0.03,  $P = 0.04$ ; HCAZ: 0.17 vs. 0.42,  $P = 0.02$ ), but no difference in weight-for-age z-score (WAZ). There were no significant differences between those with and without tenofovir exposure at age 1 year when defining low LAZ or HCAZ as  $\leq 1.5$  z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.<sup>19</sup> In a different U.S. study (P1025), maternal tenofovir use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants followed for 6 months, tenofovir exposure after the first trimester, relative to no exposure, was associated with being underweight (WAZ <5%) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95],  $P = 0.04$ ).<sup>20</sup>

In a cross-sectional study of 68 HIV-exposed uninfected children enrolled at ages 1 to 6 years who had *in utero* exposure to combination regimens with (N = 33) or without (N = 35) tenofovir, evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.<sup>21</sup> In contrast, a study evaluating whole body dual-energy X-ray absorptiometry scans within 4 weeks of birth among 74 infants exposed to more than 8 weeks of tenofovir *in utero* and 69 infants with no tenofovir exposures, the adjusted mean whole body bone mineral content (BMC) was significantly lower in the tenofovir group by 6.3 g ( $P = 0.004$ ) as was the whole-body-less-head BMC (-2.6 g,  $P = 0.056$ ). The duration and clinical significance of these findings require further longitudinal evaluation.<sup>22</sup>

**Excerpt from Table 7<sup>a</sup>**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Tenofovir Disoproxil Fumarate</b> (TDF) <i>Viread</i>	<u>TDF (Viread)</u> <i>Tablet:</i> • 300 mg  <i>Powder:</i> • 40 mg/1 g oral powder	<u>Standard Adult Dose</u> <i>TDF (Viread)</i> <u>Tablet:</u> • 300 mg once daily without regard to food  <u>Powder:</u> • 8 mg/kg (up to maximum 300 mg), take with food	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).  Studies in monkeys (at doses approximately 2-fold higher than that for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no effect on intrauterine growth, but data are conflicting about potential effects on growth outcomes later in infancy.
(TDF/FTC) <i>Truvada</i>	<u>Truvada:</u> • TDF 300 mg plus FTC 200 mg tablet	<i>Truvada:</i> • 1 tablet once daily without regard to food	If HBV-coinfected, it is possible that an HBV flare may occur if TDF is stopped; see <a href="#">HIV/Hepatitis B Virus Coinfection</a> .  Renal function should be monitored because of potential for renal toxicity.
(TDF/FTC/EFV) <i>Atripla</i>	<u>Atripla:</u> • TDF 300 mg plus FTC 200 mg plus EFV <sup>c</sup> 600 mg tablet	<i>Atripla:</i> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.	
(TDF/FTC/RPV) <i>Complera</i>	<u>Complera:</u> • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet	<i>Complera:</i> • 1 tablet once daily with food	
(TDF/FTC/EVG/COBI) <i>Stribild</i>	<u>Stribild:</u> • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet	<i>Stribild:</i> • 1 tablet once daily with food	
		<u>PK in Pregnancy:</u> • AUC lower in third trimester than postpartum but trough levels adequate  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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

<sup>c</sup> See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

**Key to Abbreviations:** d4T = stavudine; ddl = didanosine; PK = pharmacokinetic; ZDV = zidovudine

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## **Zalcitabine (HIVID, ddC)**

**(Last updated March 28, 2014; last reviewed March 28, 2014)**

Zalcitabine is no longer available in the United States.

## **Zidovudine (Retrovir, AZT, ZDV)**

**(Last updated August 6, 2015; last reviewed August 6, 2015)**

Zidovudine is classified as Food and Drug Administration Pregnancy Category C.

### **Animal Studies**

#### *Carcinogenicity*

Zidovudine was shown to be mutagenic in two *in vitro* assays and clastogenic in one *in vitro* and two *in vivo* assays, but not cytogenic in a single-dose *in vivo* rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats.<sup>1</sup> In mice, seven late-appearing (>19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of an animal given an intermediate dose. No vaginal tumors were found at the lowest dose. In rats, two late-appearing (>20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex in either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by area under the curve [AUC]) was approximately three times (mice) and 24 times (rats) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. How predictive the results of rodent carcinogenicity studies may be for humans is unknown.

Two transplacental carcinogenicity studies were conducted in mice.<sup>2,3</sup> In one study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestational Day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months.<sup>3</sup> The drug doses administered in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. In a second study, zidovudine was administered at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 to 18 of gestation.<sup>2</sup> There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose of zidovudine.

#### *Reproduction/Fertility*

When administered to male and female rats at doses up to seven times the usual adult dose based on body surface area, zidovudine had no effect on fertility, as judged by rates of conception. Zidovudine has been shown to have no effect on reproduction or fertility in rodents. A dose-related cytotoxic effect on preimplantation mouse embryos can occur, with inhibition of blastocyst and post-blastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.<sup>4</sup>

#### *Teratogenicity/Developmental Toxicity*

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity, as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times and in rabbits 12 to 87 times mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure

resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations (estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Increased fetal resorption occurred in pregnant rats and rabbits treated with zidovudine doses that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. No other developmental anomalies were reported. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

## Human Studies in Pregnancy

### *Pharmacokinetics*

Zidovudine pharmacokinetics are not significantly altered by pregnancy, and standard adult doses are recommended.<sup>5,6</sup>

### *Placental and Breast Milk Passage*

Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal-blood ratios of about 0.80. The ratio of zidovudine in amniotic fluid to that in maternal plasma is 1.5.<sup>7</sup> Zidovudine is excreted into human breast milk with breast milk-to-maternal-plasma zidovudine concentration ratios ranging from 0.44 to 1.35. No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.<sup>8-10</sup>

### *Teratogenicity/Developmental Toxicity*

In PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups, and no specific patterns of defects were seen.<sup>5,11</sup> Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.<sup>12,13</sup> A previous report from the Women and Infants Transmission Study described a 10-fold increased risk of hypospadias, but this finding was not confirmed in a more detailed analysis.<sup>14,15</sup> The French Perinatal Cohort reported that first-trimester zidovudine exposure was associated with congenital heart defects (2.3%, or 74/3,267; adjusted odds ratio = 2.2 [95% confidence interval (CI), 1.3–3.7]).<sup>16</sup> In the PHACS/SMARTT cohort, there was no association between first-trimester exposure and congenital anomalies.<sup>17</sup> In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to zidovudine have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased incidence of defects in the more common classes, including the genitourinary system. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.2% (129 of 4,034 births; 95% CI, 2.7%–3.8%), compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.<sup>18</sup>

Cancer has been observed no more frequently among zidovudine-exposed infants than among other HIV-exposed or HIV-unexposed infants in a long-term follow-up study for the original PACTG 076 study,<sup>19</sup> in prospective cohort studies,<sup>20</sup> and in matches between HIV surveillance and cancer registries.<sup>21,22</sup>

### *Other Safety Data*

In the placebo-controlled perinatal trial PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received a placebo, based on follow-up through 4 years postpartum.<sup>23</sup>

No differences in immunologic, neurologic, or growth parameters were seen between PACTG 076 infants with *in utero* zidovudine exposure and those who received a placebo, based on nearly 6 years of follow-up.<sup>11,19</sup>

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors (NRTIs) during pregnancy has been described in some case reports, case series, prospective cohorts, and surveillance systems, but not in others. The result of the dysfunction, although fatal in a few cases, is more often asymptomatic and self-limited (e.g., leukopenia, anemia). At present, while a recognized possibility, the risk of NRTI-associated mitochondrial dysfunction in these mother-infant pairs does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.

**Excerpt from Table 7<sup>a</sup>**

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Zidovudine</b> (AZT, ZDV) <i>Retrovir</i>	<u>ZDV (Retrovir)</u> <i>Capsule:</i> • 100 mg <i>Tablet:</i> • 300 mg <i>Oral Solution:</i> • 10 mg/mL <i>Intravenous Solution:</i> • 10 mg/mL	<u>Standard Adult Dose(s)</u> <i>ZDV (Retrovir):</i> • 300 mg BID or 200 mg TID, without regard to food  <u>Active Labor:</u> • 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).
(ZDV/3TC) <i>Combivir</i>	<u>Combivir:</u> • ZDV 300 mg plus 3TC 150 mg tablet	<i>Combivir:</i> • Tablet twice daily, without regard to food	
(ZDV/3TC/ABC) <i>Trizivir</i>	<u>Trizivir:</u> • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	<i>Trizivir:</i> • Tablet twice daily, without regard to food  <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy.  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, 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 Abbreviations:** 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; IV = intravenous; PK = pharmacokinetic; TID = three times a day; ZDV = zidovudine

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