



**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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# Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

## 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 reverse transcriptase inhibitors (NRTIs) zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleotide NRTI tenofovir disoproxil fumarate (TDF). The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. TDF, 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 Infants Exposed to Antiretroviral Drugs](#).

### *Abacavir (Ziagen, ABC)*

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The available human and animal data suggest that abacavir does not increase the risk of major birth defects overall compared with the background rate.<sup>1</sup>

#### **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.<sup>1</sup>

##### *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/Adverse Pregnancy Outcomes*

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 (i.e., increased resorptions and decreased fetal body weight) occurred with administration of abacavir 500 mg/kg/day to pregnant rodents. The offspring of female rats were treated with abacavir 500 mg/kg, 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 rabbits, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to abacavir 700 mg/kg (about 8.5 times that of human therapeutic exposure).<sup>1</sup>

#### *Placental and Breast Milk Passage*

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

### **Human Studies in Pregnancy**

#### *Pharmacokinetics*

In pregnant women, pharmacokinetic (PK) studies of abacavir 300 mg twice daily<sup>2</sup> and 600 mg daily concluded<sup>3</sup> that the PKs during pregnancy are equivalent to the PKs observed during the postpartum period. A population PK study (that analyzed 266 plasma samples from 150 pregnant women) found no effect of any co-variate (including age, body weight, pregnancy or gestational age) on abacavir PKs.<sup>4</sup> Thus, no dose adjustment for abacavir is needed during pregnancy.

#### *Placental and Breast Milk Passage*

Placental transfer of abacavir is high, with ratios of cord blood to maternal plasma concentration at delivery of approximately 1.0.<sup>2,5</sup> In the Mma Bana study,<sup>6</sup> the median breast milk-to-plasma ratio for abacavir was 0.85 in the 15 women tested at 1 month postpartum, and the drug was detected in the plasma of one out of nine breastfeeding infants whose mothers were receiving abacavir.

#### *Teratogenicity/Adverse Pregnancy Outcomes*

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 1.5-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 **2.83%** (32 out of 1,131 births; 95% CI, 1.94% to **3.97%**).<sup>7</sup> This prevalence is similar to the prevalence of birth defects in the U.S. population, which is 2.72%, according to Centers for Disease Control and Prevention surveillance. First-trimester exposure to abacavir was not associated with birth defects in the SMARTT study (adjusted odds ratio [aOR] 0.94 [0.53–1.65]),<sup>8</sup> in the French Perinatal Study (aOR 1.01 [0.73–1.41]),<sup>9</sup> or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99 [0.34–2.87]).<sup>10</sup>

#### *Safety*

Serious hypersensitivity reactions have been associated with abacavir therapy in nonpregnant 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 the highest risk of hypersensitivity reactions and should not receive abacavir; HLA screening should be done before initiation of abacavir. Two meta-analyses have confirmed the association between this genotype and the hypersensitivity reaction.<sup>11,12</sup>

In the PHACS/SMARTT cohort (median follow-up: 2.4 years), after adjusting for birth cohort and other factors, use of abacavir by the mother during pregnancy led to no increase in the likelihood of adverse events for the infant in the following domains: metabolic, growth and development, cardiac, neurological, neurodevelopmental.<sup>13</sup>

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

**Note:** When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Abacavir</b> (ABC) <i>Ziagen</i> (ABC/3TC) <i>Epzicom</i> (ABC/3TC/ZDV) <i>Trizivir</i> (ABC/DTG/3TC) <i>Triumeq</i> <b>Note:</b> Generics are available for some formulations.	<u>ABC (Ziagen)<sup>d</sup></u> <i>Tablet:</i> • 300 mg <i>Solution:</i> • 20 mg/mL <u>ABC/3TC (Epzicom)<sup>d</sup></u> • ABC 600 mg plus 3TC 300 mg tablet <u>ABC/3TC/ZDV (Trizivir)<sup>d</sup></u> • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet <u>ABC/DTG/3TC (Triumeq):</u> • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet	<u>Standard Adult Doses</u> <i>ABC (Ziagen):</i> • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food <i>ABC/3TC (Epzicom):</i> • 1 tablet once daily without regard to food <i>ABC/3TC/ZDV (Trizivir):</i> • 1 tablet twice daily without regard to food <i>ABC/DTG/3TC (Triumeq):</i> • 1 tablet daily without regard to food <u>Dosing in Pregnancy:</u> • No change in dose indicated. <u>PK in Pregnancy:</u> • PK not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG).	High placental transfer to fetus. <sup>b</sup> No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). HSRs occur in approximately 5% to 8% of nonpregnant individuals. A small percentage of reactions are fatal, and these fatal reactions are usually associated with re-challenge. Rate of reactions during 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 HSR.

<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

<sup>d</sup> Generic formulation available.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; HSR = hypersensitivity reactions; PK = pharmacokinetic; ZDV = zidovudine

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