



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 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 the [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) and [Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants](#) section.

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.¹

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.¹

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 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).¹

Placental and Breast Milk Passage

Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.¹

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of 300 mg twice daily and² 600 mg daily concluded³ that the PK during pregnancy is equivalent to postpartum. A population PK study (266 samples from 150 pregnant women) found no effect of any co-variate (including age, body weight, pregnancy or gestational age) on abacavir PK.⁴ Thus, no dose adjustment for abacavir is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of abacavir is high, with cord blood-to-maternal-plasma-concentration ratios at delivery of approximately 1.0.^{2,5} In the Mma Bana study,⁶ 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/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry (APR), 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 APR, the prevalence of birth defects was 2.98% (30 of 1007 births; 95% CI, 2.01% to 4.23%) compared with 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁷ There was no association of birth defects with first-trimester exposure to abacavir in the SMARTT study (aOR 0.94 [0.53–1.65]),⁸ in the French Perinatal Study (aOR 1.01, [0.73–1.41]),⁹ or in a series of 897 births to women with HIV in Spain between 2000 and 2009 (aOR 0.99, [0.34–2.87]).¹⁰

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 and should not receive abacavir; HLA screening should be done before initiation of abacavir. Two meta-analyses have confirmed the association of this genotype and the hypersensitivity reaction.^{11,12}

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.¹³

Excerpt from Table 9^a

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
Abacavir (ABC) <i>Ziagen</i> (ABC/3TC) <i>Epzicom</i> (ABC/3TC/ZDV) <i>Trizivir</i> (ABC/3TC/DTG) <i>Triumeq</i>	ABC (Ziagen):^e <i>Tablet:</i> • 300 mg <i>Solution:</i> • 20 mg/mL Epzicom:^e • ABC 600 mg plus 3TC 300 mg tablet Trizivir:^e • ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg tablet Triumeq: • ABC 600 mg plus 3TC 300 mg plus DTG 50 mg tablet	Standard Adult Doses: <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 <i>Triumeq:</i> • 1 tablet daily without regard to food PK in Pregnancy: • PK not significantly altered in pregnancy. Dosing in Pregnancy: • No change in dose indicated.	High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-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.

^a 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](#)).

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

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

^c See [Teratogenicity](#) for discussion of EFV and risks in pregnancy.

^d Only indicated for use in chronic hepatitis B virus infection in adults.

^e Generic formulation available.

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

References

1. Abacavir [package insert]. Food and Drug Administration. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020977s030_020978s034lbl.pdf.
2. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. *AIDS*. 2006;20(4):553-560. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16470119>.
3. Schalkwijk S, Colbers A, Konopnicki D, et al. The pharmacokinetics of abacavir 600 mg once daily in HIV-1-positive pregnant women. *AIDS*. 2016;30(8):1239-1244. Available at <https://www.ncbi.nlm.nih.gov/pubmed/26836789>.
4. Fauchet F, Treluyer JM, Preta LH, et al. Population pharmacokinetics of abacavir in pregnant women. *Antimicrob Agents Chemother*. 2014;58(10):6287-6289. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25070097>.
5. Chappuy H, Treluyer JM, Jullien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*. 2004;48(11):4332-4336. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15504861>.
6. Shapiro RL, Rossi S, Ogwu A, et al. Therapeutic levels of lopinavir in late pregnancy and abacavir passage into breast milk in the Mma Bana Study, Botswana. *Antivir Ther*. 2013;18(4):585-590. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23183881>.
7. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989–1 January 2016. Wilmington, NC: Registry Coordinating Center. 2016.
8. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25383770>.
9. Sibiude J, Le Chenadec J, Bonnet D, et al. *In utero* exposure to zidovudine and heart anomalies in the ANRS French Perinatal Cohort and the Nested PRIMEVA Randomized Trial. *Clin Infect Dis*. 2015. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25838291>.

10. Prieto LM, Gonzalez-Tome MI, Munoz E, et al. Birth defects in a cohort of infants born to HIV-infected women in Spain, 2000-2009. *BMC Infectious Diseases*. 2014;14:700. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25808698>.
11. Sousa-Pinto B, Pinto-Ramos J, Correia C, et al. Pharmacogenetics of abacavir hypersensitivity: A systematic review and meta-analysis of the association with HLA-B*57:01. *J Allergy Clin Immunol*. 2015;136(4):1092-1094 e1093. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25934581>.
12. Tangamornsuksan W, Lohitnavy O, Kongkaew C, et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. *J Pharm Pharm Sci*. 2015;18(1):68-76. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25877443>.
13. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at <https://www.ncbi.nlm.nih.gov/pubmed/26731758>.