Abacavir (Ziagen, ABC)

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Summary

- No dose adjustments are required for abacavir (ABC) during pregnancy.
- First-trimester exposure to ABC is not associated with increased risk of congenital abnormalities.
- HLA-B*5701 screening should be done before initiating ABC. Patients who test positive for HLA-B*5701 are at the highest risk of hypersensitivity reactions and should not receive ABC.

Human Studies in Pregnancy

Pharmacokinetics

In pregnant women, pharmacokinetic (PK) studies of ABC 300 mg twice daily[1] and ABC 600 mg once daily[2] showed that the PKs during pregnancy are equivalent to the PKs observed during the postpartum period. A population PK study (analyzing 266 plasma samples from 150 pregnant women) found no effect of any covariate (including age, body weight, pregnancy, or gestational age) on ABC PKs.[3] Thus, no dose adjustment for ABC is needed during pregnancy.

Placental and Breast Milk Passage

Placental transfer of ABC is high, with ratios of ABC concentration in cord blood–to–ABC concentration in maternal plasma at delivery of approximately 1.0.[1,4] In the Mma Bana study,[5] the median breast milk–to–plasma ratio for ABC 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 ABC. In the Swiss Mother and Child HIV Cohort nested study, ABC was measurable in four breastfeeding infants; the relative infant dose was 0.34%.[6]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to ABC to detect at least a 1.5-fold increase in the risk of overall birth defects and at least a twofold increase in the risk of cardiovascular and genitourinary defects (which are the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with ABC. Among the cases of first-trimester ABC exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.2% (47 infants out of 1,455 live births; 95% confidence interval, 2.4% to 4.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[7] First-trimester exposure to ABC was not associated with birth defects in the Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) study (adjusted odds ratio [aOR] 0.94, 0.53–1.65),[8] in the French Perinatal Cohort (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]

Pregnancy outcomes were similar between pregnant women who received an ABC/lamivudine (3TC) backbone (n = 252) and women who received a tenofovir disoproxil fumarate/emtricitabine

backbone (n = 661) in the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy. However, total cholesterol levels were higher in the group that received ABC.[11]

Ten percent of participants (711 pregnancies) received ABC plus 3TC in the European Pregnancy Paediatric HIV Cohort Collaboration (EPPICC) study group. The proportions of preterm deliveries and small-for-gestational-age infants that occurred among women who received ABC were similar to those seen among women who received other antiretroviral drugs.[12]

Other Safety Information

Serious hypersensitivity reactions (HSRs) have been associated with ABC therapy in nonpregnant adults, but these reactions rarely have been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. ABC **should not be restarted** following an HSR 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 HSRs and should not receive ABC; HLA-B*5701 screening should be done before initiating ABC. Two meta-analyses have confirmed the association between this genotype and the HSR.[13,14]

After adjusting for birth cohort and other factors, the Pediatric HIV/AIDS Cohort Study (PHACS)/ SMARTT study (which followed participants for a median of 2.4 years) reported no increases in the likelihood of metabolic, cardiac, neurological, growth and development, or neurodevelopmental adverse events among infants whose mothers took ABC during pregnancy.[15]

Animal Studies

Carcinogenicity

Preputial and clitoral gland tumors and malignant hepatic tumors were seen in rodents at exposures that were 6 to 32 times those observed in humans who received the recommended dose.[16]

Reproduction/Fertility

No effect on reproduction or fertility in rodents was seen at doses that were about eight times the exposures seen in humans who received the recommended dose.[16]

Teratogenicity/Adverse Pregnancy Outcomes

Decreased fetal body weight and reduced crown–rump length were seen in rats treated during organogenesis. An increased number of resorptions and an increased incidence of stillbirths occurred among rats treated from embryo implantation through weaning of the pups. No developmental toxicities and no increases in fetal malformations occurred in pregnant rabbits at up to the highest dose evaluated, resulting in exposures approximately nine times the human exposure at the recommended dose.[16]

Placental and Breast Milk Passage

ABC crosses the placenta and is excreted into the breast milk of lactating rats.[16]

Excerpt from Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Abacavir (ABC) *Ziagen* (ABC/3TC) *Epzicom* (ABC/DTG/3TC) *Triumeq* (ABC/3TC/ZDV) *Trizivir* Note: Generic products are available for some formulations.	ABC (Ziagen)[c] *Tablet* • 300 mg *Oral Solution* • 20 mg/mL ABC/3TC (Epzicom)[c] • ABC 600-mg/ 3TC 300-mg tablet ABC/DTG/3TC (Triumeq) • ABC 600-mg/ DTG 50-mg/ 3TC 300-mg tablet ABC/3TC/ZDV (Trizivir)[c] • ABC 300-mg/ 3TC 150-mg/ ZDV 300-mg tablet	Pregnancy *PKs in Pregnancy* • PKs not significantly altered in pregnancy *Dosing in Pregnancy* • No change in dose indicated For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, ZDV, DTG). Standard Adult Doses *ABC (Ziagen)* • ABC 300 mg twice daily or ABC 600 mg once daily, without regard to food *ABC/3TC (Epzicom)* • One tablet once daily without regard to food *ABC/DTG/3TC (Triumeq)* • One tablet once daily without regard to food *ABC/3TC/ZDV (Trizivir)* • One tablet twice daily without regard to food	High placental transfer to fetus[b] 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 a patient's status **should be documented as negative** before initiating ABC. Patients should be educated regarding symptoms of HSR.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 12).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

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

[c] Generic product available

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DTG = dolutegravir; HSR = hypersensitivity reaction; PK = pharmacokinetic; ZDV = zidovudine

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