Zidovudine (Retrovir, ZDV)

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Summary

- No dose adjustments are required for zidovudine (ZDV) during pregnancy.
- First-trimester exposure to ZDV is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

ZDV pharmacokinetics (PK) are not significantly altered by pregnancy, and standard adult doses are recommended during pregnancy.[1,2] A population PK analysis that evaluated oral and intravenous (IV) ZDV doses during pregnancy and labor found high fetal exposure to ZDV with current IV intrapartum dosing regimens. Simulations suggested that reduced intrapartum ZDV dosing regimens might provide lower but still adequate fetal ZDV exposures.[3] However, standard dosing of IV ZDV during labor continues to be recommended for people with unknown or elevated viral loads. In pregnant women, as with nonpregnant adults, intracellular ZDV triphosphate concentrations do not vary with plasma concentrations over a wide range of plasma ZDV concentrations.[4]

Placental and Breast Milk Passage

ZDV rapidly crosses the human placenta, achieving cord blood–to–maternal plasma ratios of about 0.80. The ratio of ZDV in amniotic fluid to ZDV in maternal plasma[5] is 1.5. ZDV is excreted into human breast milk, with breast milk–to–maternal plasma ZDV concentration ratios ranging from 0.44 to 1.35. No ZDV was detectable in the plasma of nursing infants who were exposed to ZDV via only breast milk.[6-8]

Teratogenicity/Adverse Pregnancy Outcomes

In Pediatric AIDS Clinical Trials Group 076 (PACTG 076), the incidence of minor and major congenital abnormalities was similar between groups that received either ZDV or placebo, and no specific patterns of defects were seen.[1,9] Similarly, no increase in the incidence of birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.[10,11] A previous report from the Women and Infants Transmission Study described a 10-fold increase in the risk of hypospadias among infants who were exposed to ZDV, but this finding was not confirmed in a more detailed analysis.[12,13] In the Pediatric HIV/AIDS Cohort Study/Surveillance Monitoring for Antiretroviral Therapy Toxicities (PHACS/SMARTT) study cohort, no association was identified between first-trimester exposure to ZDV and congenital anomalies.[14]

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for ZDV and other ARV drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to ZDV in humans to be able to detect at least a 1.5-fold increase in the risk of overall birth defects and a twofold increase in the risk of defects in the more common classes, including the cardiovascular and genitourinary systems. No such increase in the risk of birth defects has been observed in infants who were exposed to ZDV. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report

provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to ZDV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births). Similarly, a series of 897 infants exposed to HIV born in Spain between 2000 and 2009 reported[15] no increase in the incidence of birth defects among infants with first-trimester ZDV exposure (adjusted odds ratio [aOR] 1.21, 0.56–2.63). A Bayesian analysis that combined a meta-analysis with data from Medicaid Analytic eXtract found no association between ZDV exposure during the first trimester and most congenital malformations.[16]

The French Perinatal Cohort reported that first-trimester ZDV exposure was associated with congenital heart defects (1.5% of 3,262 exposures vs. 0.7% of non-exposures; aOR 2.2; 95% CI, 1.5–3.2). However, an analysis[17] of cardiac defects among all prenatal infants exposed to ZDV in the APR (n = 13,073) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to ZDV-containing regimens (9 of 4,000 infants exposed during the first trimester, rate 0.23; 22 of 9,047 infants with later exposure, rate 0.24, $P = 1.00$) and regimens that did not contain ZDV (2 of 1,839 infants exposed during the first trimester, rate 0.11; 3 of 538 infants with later exposure, rate 0.56, $P = 0.08$).

In the ANRS 135 PRIMEVA trial, mothers were randomized to receive antepartum treatment with ZDV plus lamivudine plus lopinavir/ritonavir (LPV/r) or LPV/r alone. Female infants of women in the first group had a higher left ventricular shortening fraction at 1 month and increased posterior wall thickness at 1 year—suggestive of myocardial remodeling—when compared with infants whose mothers received LPV/r alone.[18] In a study that performed fetal echocardiography on 42 fetuses who had been exposed to HIV but were not infected and 84 fetuses who had not been exposed to HIV, infants born to mothers who received ZDV were more likely to have thicker myocardial walls and smaller left ventricular cavities than other infants, regardless of HIV exposure. Maternal ZDV treatment was the only factor significantly associated with fetal cardiac changes.[19] Another study by the same authors reported the presence of hypertrophic myocardium and signs of increased mitochondrial content in the cord blood of infants who had been exposed to HIV. In this study, both conditions were associated with maternal use of ZDV during pregnancy.[20] A small follow-up study by the same authors identified hypertension among infants with *in utero* exposure to ZDV.[21]

Cancer has not been observed more frequently among infants exposed to ZDV compared with other infants exposed to HIV or unexposed to HIV in a long-term follow-up study for the original PACTG 076 study,[22] in prospective cohort studies,[23] and in matches between HIV surveillance and cancer registries.[24,25]

Other Safety Information

Mitochondrial dysfunction in mothers and infants exposed to nucleoside reverse transcriptase inhibitors during pregnancy has been reported in case reports and case series and in some, but not all, prospective cohorts and surveillance systems. As part of its surveillance for such dysfunction, the PHACS/SMARTT cohort used a “trigger-based design” in which several domains (e.g., metabolic) had predetermined “triggers.” Children who met the definition of a trigger were further investigated to determine whether they had met the definition of a “case” in that domain. The study found that after adjusting for birth cohort and other factors, ZDV use was associated with an increased risk of meeting the study’s definition of a metabolic case (adjusted relative risk 1.69; 95% CI, 1.08–2.64).[26,27]

Animal Studies

Carcinogenicity

Late-appearing, non-metastasizing vaginal squamous cell carcinomas were seen in mice and rats, predominantly among those given the highest doses (approximately 3–24 times the estimated human exposure with a dose of 100 mg every 4 hours).[28]

With transplacental exposure followed by postnatal exposure in mice (approximately three times the exposure of humans receiving the recommended dose), vaginal tumors were noted.[28]

One group of authors attributed the vaginal tumors in ZDV-treated mice to vaginal exposure from high urine ZDV concentrations.[29]

Reproduction/Fertility

ZDV has been shown to have no effect on reproduction or fertility in rodents.[28]

Teratogenicity/Adverse Pregnancy Outcomes

Embryotoxicity was seen in rats exposed preconceptionally and during gestation (exposure was approximately 33 times higher than that seen in humans receiving the recommended clinical dose), and rabbits exposed gestationally (approximately 108 times the estimated exposure of humans receiving the recommended dose).[28]

In an additional teratology study in rats, a dose of ZDV 3,000 mg/kg per day (which was very near the median lethal oral dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak ZDV plasma concentrations that were 350 times peak human plasma concentrations (the estimated area under the curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day). No evidence of teratogenicity was seen in this experiment at doses of ZDV 600 mg/kg per day or less.[28]

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**
Zidovudine (ZDV) *Retrovir* (ZDV/3TC) **Note:** Generic products are available for all formulations.	**ZDV (Retrovir)** *Capsule* • 100 mg *Tablet* • 300 mg *Oral Solution* • 10 mg/mL *IV Solution* • 10 mg/mL **ZDV/3TC** • ZDV 300-mg/ 3TC 150-mg tablet •	**Pregnancy** *PK in Pregnancy* • PK not significantly altered in pregnancy *Dosing in Pregnancy* • No change in dose indicated • Patients in active labor should receive ZDV 2 mg/kg IV as a loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until birth. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC). **Standard Adult Doses** *ZDV (Retrovir)* • ZDV 300 mg twice daily or ZDV 200 mg three times a day without regard to food *ZDV/3TC* • 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) **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with ZDV is contraindicated.

[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).

[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

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; IV = intravenous; PK = pharmacokinetic; ZDV = zidovudine

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