



**Recommendations for the Use of Antiretroviral Drugs in
Pregnant Women with HIV Infection and Interventions to Reduce
Perinatal HIV Transmission in the United States**

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Zidovudine (Retrovir, AZT, ZDV)

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Available evidence does not suggest that zidovudine use by pregnant women is associated with an increased risk of adverse fetal or pregnancy outcomes.¹

Animal Studies

Carcinogenicity

Zidovudine was shown to be mutagenic in two *in vitro* assays and clastogenic in one *in vitro* assay 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.² In mice, seven late-appearing (>19 months) vaginal neoplasms (five nonmetastasizing squamous cell carcinomas, one squamous cell papilloma, and one 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), nonmetastasizing 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.¹

Two trans-placental carcinogenicity studies were conducted in mice.^{3,4} 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.⁴ 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 (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 to 18 of gestation.³ 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.⁵

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (expressed as AUC) approximately 33 times higher than human exposures at the recommended clinical dose. However, no embryotoxicity was observed after administration to pregnant rats during organogenesis at doses that produced AUC approximately 117 times higher than clinical exposures. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced exposures approximately 108 times higher than the clinical exposure. No embryotoxicity was observed at doses that produced exposures approximately 23 times higher than clinical exposures.¹

In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 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.

Human Studies in Pregnancy

Pharmacokinetics

Zidovudine pharmacokinetics (PK) are not significantly altered by pregnancy, and standard adult doses are recommended.^{6,7} A population PK analysis following oral and intravenous (IV) zidovudine doses during pregnancy and labor found high fetal exposure to zidovudine with current IV intrapartum dosing regimens. Simulations from this modeling suggested that reduced intrapartum zidovudine dosing regimens might provide lower but still adequate fetal zidovudine exposures.⁸ However, standard dosing of IV zidovudine during labor continues to be recommended. In pregnant women, as with nonpregnant adults, intracellular zidovudine triphosphate concentrations do not vary with plasma concentrations, over a wide range of plasma zidovudine concentrations.⁹

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 1.5.¹⁰ 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 nursing infants who received zidovudine only via breast milk.¹¹⁻¹³

Teratogenicity/Adverse Pregnancy Outcomes

In PACTG 076, the incidence of minor and major congenital abnormalities was similar between groups that received either zidovudine or placebo, and no specific patterns of defects were seen.^{6,14} Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.^{15,16} A previous report from the Women and Infants Transmission Study described a 10-fold increased risk of hypospadias among infants who received zidovudine, but this finding was not confirmed in a more detailed analysis.^{17,18} In the PHACS/SMARTT cohort, there was no association between first-trimester exposure to zidovudine and congenital anomalies.¹⁹ 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 cardiovascular and genitourinary systems. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.2% (134 of 4,178 births; 95% CI, 2.7% to 3.8%), compared with a total prevalence in the U.S. population of 2.72%, based on Centers for Disease Control and Prevention surveillance.²⁰ Similarly, a series of 897 infants exposed to HIV born in Spain during 2000 through 2009 reported no increase in birth defects among infants with first-trimester zidovudine exposure (adjusted odds ratio [aOR] 1.21, 0.56–2.63).²¹ **A Bayesian analysis that combined a meta-analysis with data from Medicaid Analytic eXtract found no association between zidovudine exposure during the first trimester and most congenital malformations.**²²

The French Perinatal Cohort reported that first-trimester zidovudine exposure was associated with congenital heart defects (1.5% of 3,262 exposures vs. 0.7% of nonexposures; aOR 2.2, 95% CI, 1.5–3.2). However, an analysis of cardiac defects among all prenatal zidovudine-exposed infants in the Antiretroviral Pregnancy Registry (n = 13,703) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to zidovudine-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 zidovudine-non-containing regimens (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).²³

In the PRIMEVA trial, mothers were randomized to receive antepartum treatment with zidovudine/lamivudine/lopinavir/ritonavir or lopinavir/ritonavir (LPV/r). 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 to infants whose mothers received LPV/r alone.²⁴ In a study that performed fetal echocardiography on 42 fetuses who had been exposed to HIV but who were not infected and 84 fetuses without HIV exposure, multivariate analysis revealed that maternal zidovudine treatment was associated with thicker myocardial walls and smaller left ventricular cavities among infants exposed to zidovudine compared to other infants with or without HIV exposure. Maternal zidovudine treatment was the only factor significantly associated with fetal cardiac changes.²⁵

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,²⁶ in prospective cohort studies,²⁷ and in matches between HIV surveillance and cancer registries.^{28,29}

Other Safety Information

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.³⁰

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.^{14,26}

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, the risk of NRTI-associated mitochondrial dysfunction in these mother-infant pairs, while a recognized possibility, does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.

The PHACS/SMARTT cohort used a “trigger-based design” in which several domains (e.g., metabolic) had predetermined “triggers;” children meeting the definition of a trigger were further investigated to determine if they had met the definition of a “case” in that domain. The study found that after adjusting for birth cohort and other factors, zidovudine was associated with increased risk of meeting the study’s definition of a metabolic case (adjusted relative risk 1.69; 95% CI, 1.08–2.64).^{31,32}

Excerpt from Table 10^a

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
Zidovudine (ZDV) <i>Retrovir</i> (ZDV/3TC) <i>Combivir</i> (ZDV/ABC/3TC) <i>Trizivir</i> Note: Generics are approved for all formulations.	<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>ZDV/3TC (Combivir):</u> • ZDV 300 mg plus 3TC 150 mg tablet <u>ZDV/ABC/3TC (Trizivir):</u> • ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet	<u>Standard Adult Dose</u> <i>ZDV (Retrovir):</i> • ZDV 300 mg BID or ZDV 200 mg TID without regard to food <u>Active Labor:</u> • ZDV 2 mg/kg IV loading dose, followed by ZDV 1 mg/kg/hour continuous infusion from beginning of active labor until delivery <i>Combivir:</i> • 1 tablet twice daily without regard to food <i>Trizivir:</i> • 1 tablet twice daily without regard to food <u>Dosing in Pregnancy:</u> • No change in dose is indicated. <u>PK in Pregnancy:</u> • PK is not significantly altered in pregnancy. • For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC)	High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).

^a Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 8](#)).

^b 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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral BID = twice daily; FDC = fixed-dose combination; IV = intravenous; PK = pharmacokinetic; TID = three times a day; ZDV = zidovudine

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