

Zidovudine (Retrovir, ZDV)

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Animal Studies

Carcinogenicity

Zidovudine (ZDV) 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 of ZDV have been performed in mice and rats.¹ 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 in animals given 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 (in mice) and 24 times (in rats) the estimated human exposure at the recommended therapeutic dose of ZDV 100 mg every 4 hours. The predictive value of rodent carcinogenicity studies for adverse effects in humans is unknown.²

Two trans-placental carcinogenicity studies were conducted in mice.^{3,4} In one study, ZDV was administered at doses of 20 mg/kg per day or 40 mg/kg per 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 ZDV exposures approximately three times the estimated exposure for humans who receive the recommended dose. After 24 months, an increase in the incidence of vaginal tumors was noted, with no increase in the incidence of tumors in the liver, 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, ZDV was administered at the maximum tolerated doses of 12.5 mg per day or 25 mg per day (approximately 1,000 mg/kg of nonpregnant body weight or approximately 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 ZDV.

Reproduction/Fertility

ZDV had no effect on fertility when it was administered to male and female rats at doses up to seven times the usual adult dose based on body surface area; in this instance, fertility was judged by rates of conception. ZDV 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 observed at ZDV concentrations similar to levels achieved with human therapeutic doses.⁵

Teratogenicity/Adverse Pregnancy Outcomes

In animal reproduction studies, administration of oral ZDV to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposures (expressed as AUC) approximately 33 times higher than the exposures observed in humans who received the recommended clinical dose. However, no embryotoxicity was observed in pregnant rats during organogenesis at exposures that were approximately 117 times higher than clinical exposures. Embryotoxicity occurred in pregnant rabbits that received oral ZDV during organogenesis at doses that produced exposures approximately 108 times higher than the exposure observed in humans who received the recommended dose. No embryotoxicity was observed at doses that produced exposures approximately 23 times higher than the exposures observed in humans who received the recommended dose of ZDV.²

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 (estimated 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.

Human Studies in Pregnancy

Pharmacokinetics

ZDV pharmacokinetics (PKs) are not significantly altered by pregnancy, and standard adult doses are recommended during pregnancy.^{6,7} 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.⁸ However, standard dosing of IV ZDV during labor continues to be recommended for women 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.⁹

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 is 1.5.¹⁰ 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 only exposed to ZDV 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 ZDV or placebo, and no specific patterns of defects were seen.^{6,14} Similarly, no increase in the incidence of 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 increase in the risk of hypospadias among infants who were exposed to ZDV, 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 ZDV and congenital anomalies.¹⁹

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ZDV have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a two fold increase in 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. With first-trimester ZDV exposure, the prevalence of birth defects was 3.2% (134 of 4,196 births; 95% confidence interval [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 the incidence of birth defects among infants with first-trimester ZDV 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 ZDV exposure during the first trimester and most congenital malformations.²²

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 nonexposures; aOR 2.2, 95% CI, 1.5–3.2). However, an analysis of cardiac defects among all prenatal ZDV-exposed infants in the Antiretroviral Pregnancy Registry (n= 13,073) reported no difference in the prevalence of ventricular septal defect and congenital heart defects among infants exposed to ZDV-containing regimens (nine 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 (two of 1,839 infants exposed during the first trimester, rate 0.11; three 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 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 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 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.²⁵ 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.²⁶

Cancer has been observed no more frequently among ZDV-exposed infants than among other HIV-exposed or HIV-unexposed infants in a long-term follow-up study for the original PACTG 076 study,²⁷ in prospective cohort studies,²⁸ and in matches between HIV surveillance and cancer registries.^{29,30}

Other Safety Information

In the placebo-controlled perinatal trial PACTG 076, no difference in disease progression was seen between women who received ZDV and those who received a placebo during 4 years of follow-up postpartum.³¹

No differences in immunologic, neurologic, or growth parameters were seen between PACTG 076 infants with *in utero* ZDV exposure and those who received a placebo during nearly 6 years of follow-up.^{14,27}

Mitochondrial dysfunction in mothers and infants who were 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 is a recognized possibility; however, this risk does not outweigh the clear benefit of these drugs in preventing perinatal HIV transmission.²

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, 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).^{32,33}

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 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) <i>Retrovir</i> (ZDV/3TC) <i>Combivir</i> (ZDV/ABC/3TC) <i>Trizivir</i> Note: Generic products are available for all formulations.	ZDV (Retrovir) <i>Capsule:</i> <ul style="list-style-type: none"> 100 mg <i>Tablet:</i> <ul style="list-style-type: none"> 300 mg <i>Oral Solution:</i> <ul style="list-style-type: none"> 10 mg/mL <i>IV Solution:</i> <ul style="list-style-type: none"> 10 mg/mL ZDV/3TC (Combivir): <ul style="list-style-type: none"> ZDV 300 mg/3TC 150 mg tablet ZDV/ABC/3TC (Trizivir): <ul style="list-style-type: none"> ZDV 300 mg/ABC 300 mg/3TC 150 mg tablet 	Standard Adult Doses <i>ZDV (Retrovir):</i> <ul style="list-style-type: none"> ZDV 300 mg twice daily or ZDV 200 mg three times a day without regard to food 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 delivery. <i>ZDV/3TC (Combivir):</i> <ul style="list-style-type: none"> One tablet twice daily without regard to food <i>ZDV/ABC/3TC (Trizivir):</i> <ul style="list-style-type: none"> One tablet twice daily without regard to food Pregnancy <i>PKs in Pregnancy:</i> <ul style="list-style-type: none"> PKs not significantly altered in pregnancy. <i>Dosing in Pregnancy:</i> <ul style="list-style-type: none"> No change in dose indicated. <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., ABC, 3TC).</p>	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 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 10](#)).

^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: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; FDC = fixed-dose combination; IV = intravenous; PK = pharmacokinetic; ZDV = zidovudine

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