

## **Zidovudine (Retrovir, AZT, ZDV)**

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Zidovudine is classified as Food and Drug Administration Pregnancy Category C.

### **Animal Studies**

#### *Carcinogenicity*

Zidovudine was shown to be mutagenic in two *in vitro* assays and clastogenic in one *in vitro* 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.<sup>1</sup> In mice, 7 late-appearing (>19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 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, 2 late-appearing (>20 months), non-metastasizing 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.

Two trans-placental carcinogenicity studies were conducted in mice.<sup>2,3</sup> 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.<sup>3</sup> 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 (~1,000 mg/kg non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 to 18 of gestation.<sup>2</sup> 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.<sup>4</sup>

#### *Teratogenicity/Developmental Toxicity*

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity, as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times and in rabbits 12 to 87 times mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. 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.<sup>5,6</sup> 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.<sup>7</sup> However, standard dosing of IV zidovudine during labor continues to be recommended.

### *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.<sup>8</sup> 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 the nursing infants, who received zidovudine only via breast milk.<sup>9-11</sup>

### *Teratogenicity/Developmental Toxicity*

In PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups, and no specific patterns of defects were seen.<sup>5,12</sup> Similarly, no increase in birth defects was detected among infants enrolled in the large observational cohorts PACTG 219/219C and P1025.<sup>13,14</sup> A previous report from the Women and Infants Transmission Study described a 10-fold increased risk of hypospadias, but this finding was not confirmed in a more detailed analysis.<sup>15,16</sup> In the PHACS/SMARTT cohort, there was no association between first-trimester exposure and congenital anomalies.<sup>17</sup> 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 genitourinary system. No such increase in birth defects has been observed with zidovudine. With first-trimester zidovudine exposure, the prevalence of birth defects was 3.2% (133 of 4,113 births; 95% CI, 2.7% to 3.8%), compared with a total prevalence in the U.S. population of 2.7%, based on Centers for Disease Control and Prevention surveillance.<sup>18</sup> Similarly, a series of 897 HIV-exposed infants born in Spain during 2000 through 2009 reported no increase in birth defects among infants with first-trimester zidovudine exposure (aOR 1.21 [0.56–2.63]).<sup>19</sup>

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 non-exposures; aOR=2.2 [95% CI 1.5–3.2]). In the PRIMEVA trial, female infants of mothers randomized to antepartum treatment with zidovudine/lamivudine/lopinavir/ritonavir 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 lopinavir/ritonavir alone.<sup>20</sup> 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 (9/4,000 first trimester, rate 0.23; 22/9,047 later, rate 0.24, *P* = 1.00) and zidovudine-non-containing regimens (2/1,839 first trimester, rate 0.11; 3/538 later, rate 0.56, *P* = 0.08).<sup>21</sup>

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,<sup>22</sup> in prospective cohort studies,<sup>23</sup> and in matches between HIV surveillance and cancer registries.<sup>24,25</sup>

### *Other Safety Data*

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.<sup>26</sup>

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.<sup>12,22</sup>

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

### Excerpt from Table 8<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Zidovudine</b> (ZDV, AZT) <i>Retrovir</i>  (ZDV/3TC) <i>Combivir</i>  (ZDV/3TC/ABC) <i>Trizivir</i>	<u>ZDV (Retrovir)</u>  <i>Capsule:</i> <ul style="list-style-type: none"> <li>• 100 mg</li> </ul> <i>Tablet:</i> <ul style="list-style-type: none"> <li>• 300 mg</li> </ul> <i>Oral Solution:</i> <ul style="list-style-type: none"> <li>• 10 mg/mL</li> </ul> <i>Intravenous Solution:</i> <ul style="list-style-type: none"> <li>• 10 mg/mL</li> </ul> <u>Combivir:</u> <ul style="list-style-type: none"> <li>• ZDV 300 mg plus 3TC 150 mg tablet</li> </ul> <u>Trizivir:</u> <ul style="list-style-type: none"> <li>• ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg tablet</li> </ul>	<u>Standard Adult Dose(s)</u>  <i>ZDV (Retrovir):</i> <ul style="list-style-type: none"> <li>• 300 mg BID or 200 mg TID, without regard to food</li> </ul> <u>Active Labor:</u> <ul style="list-style-type: none"> <li>• 2 mg/kg IV loading dose, followed by 1 mg/kg/hour continuous infusion from beginning of active labor until delivery</li> </ul> <i>Combivir:</i> <ul style="list-style-type: none"> <li>• One tablet twice daily, without regard to food</li> </ul> <i>Trizivir:</i> <ul style="list-style-type: none"> <li>• One tablet twice daily, without regard to food</li> </ul> <u>PK in Pregnancy:</u> <ul style="list-style-type: none"> <li>• PK not significantly altered in pregnancy.</li> </ul> <u>Dosing in Pregnancy:</u> <ul style="list-style-type: none"> <li>• No change in dose indicated.</li> </ul>	High placental transfer to fetus. <sup>b</sup>  No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects).

<sup>a</sup> Individual antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 7](#)).

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

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

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; IV = intravenous; PK = pharmacokinetic; TID = three times a day; ZDV = zidovudine

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