Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Glossary of Terms for Supplement
Carcinogenic = producing or tending to produce cancer • Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic. • Genetic mutations and/or chromosomal damage can contribute to cancer formation.
Clastogenic = causing disruption of or breakages in chromosomes
Genotoxic = damaging to genetic material such as DNA and chromosomes
Mutagenic = inducing or capable of inducing genetic mutation
Teratogenic = interfering with fetal development and resulting in birth defects

Six nucleoside analogue reverse transcriptase inhibitors (nucleoside NRTIs) and one nucleotide reverse transcriptase inhibitor (nucleotide NRTI) are currently approved (zalcitabine is no longer available in the United States). Data are available from clinical trials in human pregnancy for the nucleoside NRTIs zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine and the nucleoside NRTI tenofovir. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. Tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base and, hence, requires only two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see NRTI Drugs and Mitochondrial Toxicity in the perinatal guidelines.

Abacavir (Ziagen, ABC) is classified as Food and Drug Administration (FDA) Pregnancy Category C.
(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies
  Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.
- Reproduction/fertility
  No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).
- Teratogenicity/developmental toxicity
  Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (increased resorptions and decreased fetal body weight) occurred with abacavir administration of 500 mg/kg/day to

pregnant rodents. The offspring of female rats were treated with 500 mg/kg of abacavir, beginning at embryo implantation and ending at weaning. In these animals, an increased incidence of stillbirth and lower body weight was seen throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. Among cases of first-trimester abacavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (25 of 823 births; 95% confidence interval [CI], 2.0%–4.5%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.[1]

- Placental and breast milk passage
  Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.
- Human studies in pregnancy
  A Phase I study of abacavir in pregnant women indicates that the AUC drug concentration during pregnancy was similar to that at 6 to 12 weeks postpartum and in non-pregnant individuals.[2] Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults and have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will occur within hours and may include life-threatening hypotension and death.

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Didanosine (Videx, ddI) is classified as FDA Pregnancy Category B.

(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies
  Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies at human exposures of 0.7 to 1.7 times in mice and 3 times in rats have been negative.
- Reproduction/fertility
  At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.
- Teratogenicity/developmental toxicity
  No evidence of teratogenicity or toxicity was observed with administration of didanosine at 12 and 14 times human exposure, respectively, in pregnant rats and rabbits. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was

4.6% (19 of 409 births; 95% CI, 2.8%–7.2%) compared with 2.7% in the U.S. population, based on CDC surveillance.[1] All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be closely monitored.

- Placental and breast milk passage
  Placental transfer of didanosine was limited in a Phase I/II safety and pharmacokinetic (PK) study.[2] This was confirmed in a study of 100 HIV-infected pregnant women who were receiving NRTIs (generally as part of a two- or three-drug combination antiretroviral [ARV] regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (n = 10) was 0.38 (range 0.0–2.0) and in 15 of 24 (62%) samples, cord blood concentrations for didanosine were below the limits of detection.[3] A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. It is not known if didanosine is excreted in human breast milk.

- Human studies in pregnancy
  A Phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum.[2] The drug was well tolerated during pregnancy by the women and the fetuses. PK parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents;[4-6] the FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination. These two drugs should be prescribed together to pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

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Emtricitabine (Emtriva, FTC) is classified as FDA Pregnancy Category B.
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- Animal carcinogenicity studies
  Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 26 times the human systemic exposure at a therapeutic dose of 200 mg/day or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.

- Reproduction/fertility
  No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by AUC) approximately 60-fold higher in female mice and 140-fold higher in male mice than observed with human exposure at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  Incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice that resulted in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with emtricitabine. Among cases of first-trimester emtricitabine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (21 of 899 births; 95% CI, 1.4%–3.5%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.[1]

- Placental and breast milk passage
  Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits.[2] Emtricitabine has been shown to have excellent placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine once daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and mean ratios of cord blood/maternal emtricitabine concentrations were 1.17 ± 0.6 (n = 9).[3] When 35 women were administered 400 mg of emtricitabine in combination with tenofovir at delivery, median maternal and cord concentrations were 1.02 (0.034–2.04) and 0.74 (0.0005–1.46) mg/L, respectively.[4] Similarly, in a study of 26 women in P1026s who received emtricitabine during pregnancy, the mean cord:maternal blood ratio was 1.2 (90% CI, 1.0–1.5).[5] It is unknown if emtricitabine is excreted in human milk.

- Human studies in pregnancy
  Emtricitabine PKs have been evaluated in 18 HIV-infected pregnant women receiving antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum.[3] Emtricitabine exposure was modestly lower during the third trimester (8.6 µg*h/mL [5.2–15.9]) compared with the postpartum period (9.8 µg*h/mL [7.4–30.3]). Two-thirds (12 of 18) of pregnant women versus 100% (14 of 14) of postpartum women met the AUC target (10th percentile in non-pregnant adults). Trough emtricitabine levels were also lower during pregnancy (minimum plasma concentration [C_{min}] 52 ng/mL [14–180]) compared with the postpartum period (86 ng/mL [<10 to 306]). In another study of 35 women who received 400 mg of emtricitabine with tenofovir at delivery, median population AUC, maximum plasma concentration (C_{max}), and C_{min} were 14.3 µg*h/mL, 1,680 ng/mL, and 76 ng/mL, respectively.[4] In the P1026s study, 26 women had emtricitabine PKs assessed during the third trimester (median 35 weeks) and 22 postpartum (mean 8 weeks postpartum).[5] Comparing PKs during pregnancy with postpartum, higher emtricitabine clearance (25.0 vs. 20.6 liters/hour during pregnancy vs. postpartum, respectively) and lower 24-hour post-dose levels (0.058 vs. 0.085 mg/liter) were seen but the 24-hour post-

dose levels were well above the inhibitory concentration 50% (IC_{50}) in all patients. Thus, these changes are not believed to be large enough to warrant dosage adjustment during pregnancy.

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Lamivudine (Epivir, 3TC) is classified as FDA Pregnancy Category C.

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- Animal carcinogenicity studies
  Lamivudine has weak mutagenic activity in one *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35 to 45 times human exposure. Long-term animal carcinogenicity screening studies at 10 and 58 times human exposure have been negative in mice and rats, respectively.
- Reproduction/fertility
  Lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the offsprings' survival, growth, and development up to the time of weaning.
- Teratogenicity/developmental toxicity studies
  There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryolethality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects, such as defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with lamivudine. Among cases of first-trimester lamivudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.1% (127 of 4,088 births; 95% CI, 2.6%–3.7%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.[1]
- Placental and breast milk passage
  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations.[2] In a study of 123 mother/infant pairs, the placental transfer expressed as fetal-to-maternal AUC ratio was 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid-to-fetal AUC ratio, was 2.9.[3] Other studies have also noted amniotic fluid accumulation of

lamivudine.[4] This is likely secondary to renal excretion of lamivudine by the fetus; lamivudine diffuses from maternal to fetal blood through the placenta and the fetal kidney removes lamivudine from fetal blood and concentrates it in urine, with fetal micturition causing a rise in the concentration of lamivudine in amniotic fluid.

Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56.[5] In infants who received lamivudine only via breast milk, median plasma lamivudine concentration was 23 ng/mL (half-maximal IC_{50} of wild-type HIV against lamivudine = 0.6–21 ng/mL).

- Human studies in pregnancy

Two studies have evaluated lamivudine PKs in HIV-infected pregnant women, one evaluating drug levels in 57 mother/infant pairs on the day of delivery[4] and the other evaluating PKs in 20 women starting lamivudine/zidovudine at 38 weeks gestation.[2] These studies concluded that there was a lack of effect of pregnancy on lamivudine PKs after 38 weeks of pregnancy. In a larger study of 114 pregnant women, 123 women in labor, and 47 non-pregnant women receiving a lamivudine-containing regimen who had samples collected for therapeutic drug monitoring (given as 150 mg twice daily with zidovudine or 300 mg once daily with abacavir), data were retrospectively analyzed using a population PK approach.[3] Pregnant women had a 22% higher apparent clearance than non-pregnant and postpartum women, but this increase did not lead to subtherapeutic exposure; the level of lamivudine exposure in pregnant women, although lower than exposure in non-pregnant and parturient women, was relatively close to data reported previously for non-pregnant adults. Thus, no dose adjustment in pregnancy is necessary.

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Stavudine (Zerit, d4T) is classified as FDA Pregnancy Category C.

(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies

Stavudine is clastogenic in *in vitro* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic in doses producing exposures 39

(mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

- Reproduction/fertility
  Stavudine has not been shown to have an effect on reproduction or fertility in rodents. A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of 100 μM and of postblastocyst development at 10 μM.[1]

- Teratogenicity/developmental toxicity studies
  No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day. In rat fetuses, the incidence of a common skeletal variation—unossified or incomplete ossification of sternebra—was increased with 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times human exposure, with no effect noted at approximately 135 times human exposure. An increase in early rat neonatal mortality (birth to Day 4) occurred at 399 times human exposure, although survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with stavudine. Among cases of first-trimester stavudine exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (20 of 801 births; 95% CI, 1.5%–3.8%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.[2]

- Placental and breast milk passage
  Stavudine crosses the rat placenta *in vivo* and the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pigtailed macaques), fetal/maternal plasma concentrations were approximately 0.80.[3] Stavudine is excreted into the breast milk of lactating rats.

- Human studies in pregnancy
  A Phase I/II safety and PK study has been conducted of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332). Both drugs were well tolerated, with stavudine PKs similar to those in non-pregnant adults.[4] Data from primate studies also indicated that pregnancy did not affect the PKs of stavudine.[5]

  Lactic acidosis, in some cases fatal, has been described in pregnant women receiving the combination of didanosine and stavudine along with other ARV agents.[6-8] The FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed didanosine and stavudine in combination (see NRTI Drugs and Mitochondrial Toxicity in the perinatal guidelines). These drugs should be prescribed together for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this ARV combination in pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

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Tenofovir disoproxil fumarate (Viread, TDF) is classified as FDA Pregnancy Category B.

(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies
  Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

- Reproduction/fertility
  Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir disoproxil fumarate was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats for 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day.

- Teratogenicity/developmental toxicity
  Chronic exposure of fetal monkeys to tenofovir at a high dose of 30 mg/kg (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) from Days 20 to 150 of gestation did not result in gross structural abnormalities.[1] However, significantly lower fetal circulating insulin-like growth factor (IGF)-1 (a primary regulator of linear growth) and higher IGF binding protein-3 levels were shown and were associated with overall body weights approximately 13% lower than untreated controls. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment. Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible.

Continued administration of tenofovir at 30 mg/kg/day to infant monkeys resulted in significant growth restriction and severe bone toxicity in 2 of 8 (25%) infants and effects on bone biomarkers and defective bone mineralization in all animals. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose, exposure, age, and species specific. Abnormalities ranged from minimal decrease in bone mineral density and content (with oral dosing in rats and dogs that achieved drug exposures 6 to 10 times that achieved with therapeutic dosing in humans) to severe, pathologic osteomalacia (with subcutaneous [SQ] dosing given to monkeys). Juvenile monkeys given chronic SQ tenofovir at 30 mg/kg/day (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) developed osteomalacia, bone fractures, and marked hypophosphatemia. However, no clinical or radiologic bone toxicity was seen when juvenile monkeys received SQ dosing of 10 mg/kg/day (exposure equivalent to 8 times the AUC achieved with therapeutic dosing in humans). Evidence of nephrotoxicity was observed in newborn and juvenile monkeys given tenofovir in doses resulting in exposures 12 to 50 times higher than the human dose, based on body surface area comparisons.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to tenofovir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with tenofovir. Among cases of first-trimester tenofovir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (31 of 1,370 births; 95% CI, 1.5%–3.2%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.[2]

- Placental and breast milk passage

  Studies in rats have demonstrated that tenofovir is secreted in milk. Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta.[3] In studies of pregnant women on chronic dosing, the cord-to-maternal blood ratio ranged from 0.60 to 1.03, indicating high placental transfer.[4-7] In a study of 31 pregnant women receiving single-dose tenofovir (with and without emtricitabine) in labor, the drugs were well-tolerated and the median tenofovir cord-to-maternal blood ratio at delivery was 0.73 (range, 0.26 to 1.95).[8] In a study evaluating intracellular tenofovir levels in newborns, intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a maternal single dose of 600 mg tenofovir with 400 mg emtricitabine, but intracellular tenofovir diphosphate was detectable in only 2 (5.5%) of 36.[9] Neonatal dosing of tenofovir resulted in tenofovir and tenofovir diphosphate levels similar to those in adults.[9]

  Among women receiving a single 600-mg dose during labor, tenofovir was detectable in only 4 of 25 (16%) breast milk samples during the first week after delivery, with a median concentration of 13 (range 6–18) ng/mL.[8] In another study, 16 breast milk samples were obtained from 5 women who received 600 mg of tenofovir at the start of labor followed by 300 mg daily for 7 days. Tenofovir levels in breast milk ranged from 5.8 to 16.3 ng/mL, and nursing infants received an estimated 0.03% of the proposed oral dose of tenofovir for neonates.[10]

- Human studies in pregnancy

  A retrospective population PK study was performed on samples collected for therapeutic drug monitoring from 46 pregnant women and 156 non-pregnant women receiving combination regimens including tenofovir.[11] Pregnant women had a 39% higher apparent clearance compared with non-pregnant women, which decreased slightly but significantly with increasing age. In study P1026s, tenofovir PKs were evaluated in 19 pregnant women receiving tenofovir-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum.[4] The percentage of women with tenofovir AUC exceeding the target of 2 μg*hour/mL (the 10th percentile in non-pregnant adults) was lower in the third trimester (74%, 14 of 19 women) than postpartum (86%, 12 of 14 women) (P = .02); however, trough levels were

similar in the two groups. At the present time, standard dosing during pregnancy continues to be recommended.

A recent case series found tenofovir to be well tolerated among 76 pregnant women, with only 2 stopping therapy, 1 for rash and the other for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV uninfected.[12] A follow-up study of 20 of the tenofovir-exposed infants and 20 controls found no differences between the groups in renal function, including cystatin C levels, through age 2 years.[13] A retrospective review of 16 pregnancy outcomes in 15 heavily ARV experienced women demonstrated that tenofovir was well tolerated by the women and associated with normal growth and development in the infants.[14] In a cross-sectional study of 68 HIV-exposed uninfected infants who had *in utero* exposure to combination regimens with (N = 33) or without (N = 35) tenofovir, the incidence of low birth weight and length measurements (<10th percentile) was comparable in the two groups and evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.[15] The Pediatric HIV/AIDS Cohort Study from the United States reported on the association of tenofovir use during pregnancy with early growth parameters in 449 HIV-exposed but -uninfected infants.[16] Of 2,029 infants, 449 (21%) had *in utero* exposure to tenofovir. There was no difference at birth between those exposed to combination drug regimens with or without tenofovir for low birth weight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively). At age 1 year, infants exposed to combination regimens with tenofovir had a slight but significantly lower adjusted mean LAZ and HCAZ than those without tenofovir exposure (LAZ: -0.17 vs. -0.03, $P = .04$; HCAZ: 0.17 vs. 0.42, $P = .02$), but not lower weight-for-age z-score. However, there were no significant differences between those with and without tenofovir exposure at age 1 year when defining low LAZ or HCAZ as <-1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.

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Zalcitabine (HIVID, ddC) is no longer available in the United States.

(Last updated September 14, 2011; last reviewed July 31, 2012)

Zidovudine (Retrovir, AZT, ZDV) is classified as FDA Pregnancy Category C.

(Last updated July 31, 2012; last reviewed July 31, 2012)

- Animal carcinogenicity studies

  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.[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 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 AUC) was approximately 3 times (mouse)

and 24 times (rat) 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 transplacental carcinogenicity studies were conducted in mice.[2, 3] In one study, zidovudine was administered at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation, with postnatal dosing continuing in offspring for 24 months.[3] The drug doses administered in this study produced zidovudine exposures approximately 3 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 non-pregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 to 18 of gestation.[2] 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 level of zidovudine.

- Reproduction/fertility
  When administered to male and female rats at doses up to 7 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 postblastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses.[4]

- 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.

  Increased fetal resorption occurred in pregnant rats and rabbits treated with zidovudine doses that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. No other developmental anomalies were reported. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

  In humans, in the placebo-controlled perinatal trial 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.[5, 6] A report from the Women and Infants Transmission Study, a cohort study enrolling

women during pregnancy, described an association between first-trimester exposure to zidovudine and a 10-fold increased risk of hypospadias.[7] However, 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 increase in risk of overall birth defects and a 2-fold increase in defects in the more common classes, defects of 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 3.3% (124 of 3,789 births; 95% CI, 2.7%–3.9%) compared with a total prevalence in the U.S. population of 2.7%, based on CDC surveillance.[8]

- Placental and breast milk passage
  Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. Zidovudine is excreted into human breast milk. In one study in Kenya in 67 mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, zidovudine concentration in the breast milk of mothers averaged 9 ng/mL and the ratio of breast milk to maternal plasma zidovudine concentration averaged 44%.[9] No zidovudine was detectable in the plasma of the nursing infants, who received zidovudine only via breast milk.

- Human studies in pregnancy
  Zidovudine is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/kg body weight orally every 6 hours.[5, 10] Long-term data on the safety of *in utero* drug exposure in humans are not available for any ARV drug; however, short-term data on the safety of zidovudine are reassuring. In PACTG 076, no difference in disease progression was seen between women who received zidovudine and those who received placebo, based on follow-up through 4 years postpartum.[11] Additionally, no differences in immunologic, neurologic, or growth parameters were seen between infants with *in utero* zidovudine exposure and those who received placebo, based on nearly 6 years of follow-up.[6, 12]

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