Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Glossary of Terms for Supplement

Clastogenic: causing disruption or breakages of chromosomes

Mutagenic: inducing or capable of inducing genetic mutation

Genotoxic: damaging to genetic material (e.g., DNA, chromosomes)

Carcinogenic: producing or tending to produce cancer

Notes: (1) Some agents (e.g., certain chemicals or forms of radiation) are both mutagenic and clastogenic. (2) Genetic mutations and/or chromosome damage can contribute to cancer formation.

Nucleoside AND Nucleotide Analogue Reverse Transcriptase Inhibitors

There are currently six approved nucleoside analogue reverse transcriptase inhibitors (zalcitabine is no longer available in the United States). Data are available from clinical trials in human pregnancy for zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine. Tenofovir disoproxil fumarate is the first nucleotide analogue reverse transcriptase inhibitor. 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 only requires 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 **Mitochondrial Toxicity and NRTI Drugs**.

Abacavir (Ziagen®, ABC) is classified as FDA pregnancy category C.

- 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 as well as nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen at doses in rodents that were 6 to 32 times higher than human exposure at therapeutic doses.

- 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 1,000 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 to pregnant rodents at 500 mg/kg/day. The offspring of female rats treated with 500 mg/kg of abacavir beginning at embryo implantation and ending at weaning had an increased incidence of stillbirth and lower body weight 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. The prevalence of birth defects with first-trimester abacavir exposure was 3.1% (95% confidence interval [CI]: 1.9% – 4.9%) compared with total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention (CDC) surveillance of 2.7% *[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 to nonpregnant individuals *[2]*. Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in nonpregnant 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 recur within hours and may include life-threatening hypotension and death.

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Didanosine (Videx®, ddI) is classified as FDA pregnancy category B.

- 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 and 3 times in mice and rats, respectively, 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 but 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 in pregnant rats and rabbits, respectively. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted 4.4% (16/362, 95% CI: 2.5% – 7.1%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 monitored closely.
- Placental and breast milk passage
  Placental transfer of didanosine was limited in a Phase I/II safety and pharmacokinetic 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 regimen); at the time of delivery, cord-to-maternal blood ratio for didanosine (n=10) was 0.38 (range 0.0 – 2.00) and in 15/24 samples (62%), 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. Pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral 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 the combination of didanosine and stavudine (see **Mitochondrial Toxicity and NRTI Drugs**). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during 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.

- 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 the 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
  The incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice resulting 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. The prevalence of birth defects with first-trimester emtricitabine exposure was 3.2% (95% CI: 1.4% – 6.2%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 good placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine 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]*. It is unknown if emtricitabine is excreted in human milk.

- Human studies in pregnancy
  Emtricitabine pharmacokinetics have been evaluated in 18 HIV-infected pregnant women receiving highly active antiretroviral therapy (HAART) 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 (12/18) of pregnant women versus 100% (14/14) postpartum women met the AUC target (10th percentile in nonpregnant adults). Trough emtricitabine levels were also lower during pregnancy (C_{min} 52 ng/mL [14 – 180]) compared with the postpartum period (86 ng/mL [<10 – 306]). In another study of 35 women who received 400 mg of emtricitabine with tenofovir at delivery, median population AUC, C_{max}, and C_{min} were 14.3 µg*h/mL; 1,680 ng/mL; and 76 ng/mL, respectively *[4]*.

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Lamivudine (Epivir®, 3TC) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Lamivudine has weak mutagenic activity in one *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35 – 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 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.
- 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 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, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with lamivudine. The prevalence of birth defects with first-trimester lamivudine exposure was 2.9% (95% CI: 2.4% – 3.6%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk passage
  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations *[2]*. Lamivudine is excreted into human breast milk. In a study of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine in Kenya, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56 *[3]*. Their infants, who only received lamivudine via breast milk, had a median plasma lamivudine concentration of 23 ng/mL (IC_{50} of wild-type HIV against lamivudine = 0.6 – 21 ng/mL).
- Human studies in pregnancy
  A small Phase I study in South Africa evaluated the safety and pharmacokinetics of lamivudine alone or in combination with zidovudine in 20 HIV-infected pregnant women; therapy was started at 38 weeks gestation, continued through labor, and given for 1 week following birth to the infants *[2]*. The drug was well tolerated in the women at the recommended adult dose of 150 mg orally twice daily; pharmacokinetics were similar to those observed in nonpregnant adults, and no pharmacokinetic interaction with zidovudine was observed.

Zidovudine and lamivudine, given in combination orally intrapartum, were well tolerated. Lamivudine was well tolerated in the neonates, but clearance was about 50% that of older children, requiring a reduced dosing regimen (4 mg/kg/day in neonates compared to 8 mg/kg/day for infants older than 3 months). There are currently no data on the pharmacokinetics of lamivudine between 2 and 6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is not known.

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Stavudine (Zerit®, d4T) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Stavudine is clastogenic in *in vivo* 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
  No effect of stavudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of stavudine 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. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the 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. The prevalence of birth defects with first-trimester stavudine exposure was 2.7% (95% CI 1.7% – 4.2%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 pharmacokinetic study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants has been conducted (PACTG 332). Both drugs were well tolerated, with pharmacokinetics similar to those in nonpregnant adults *[4]*. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of stavudine *[5]*.

Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral 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 the combination of didanosine and stavudine (see **Mitochondrial Toxicity and NRTI Drugs**). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during 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 [DF] (Viread™) is classified as FDA pregnancy category B.

- 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 DF 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 due to 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 prior to mating and to female rats for 15 days prior to mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats (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 – 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 (IGFBP)-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 the infant monkey postnatally resulted in significant growth restriction and severe bone toxicity in 25% of 8 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 dosing given to monkeys). Juvenile monkeys given chronic subcutaneous 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 subcutaneous 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. The prevalence of birth defects with first-trimester tenofovir exposure was 2.3% 95% CI: 1.3% – 3.9%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 3 studies of pregnant women, the cord-to-maternal blood ratio ranged from 0.60 to 0.99, indicating high placental transfer *[4-6]*. In 2 studies including 21 pregnant women receiving tenofovir-based therapy, the cord-to-maternal blood ratio ranged from 0.95 to 0.99 *[4,5]*. There are no data on whether tenofovir is excreted in breast milk in humans.

- Human studies in pregnancy
  Tenofovir pharmacokinetics were evaluated in 19 pregnant women receiving tenofovir-based HAART in study P1026s at 30 to 36 weeks gestation and 6 to 12 weeks postpartum *[4]*. The percent of women with tenofovir AUC exceeding the target of 2 ug*hour/mL (the 10th percentile in nonpregnant adults) was lower in women in the third trimester (74%, 14/19) than postpartum (86%, 12/14) (p = 0.02); however, trough levels were similar in the third trimester and postpartum.

  A recent case series found tenofovir to be well tolerated among 76 pregnant women, with 2 stopping therapy, 1 for rash and 1 for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV uninfected *[7]*. A retrospective review of 16 pregnancy outcomes among 15 heavily antiretroviral experienced women demonstrated that tenofovir was well tolerated by the women and associated with normal growth and development in the infants *[8]*.

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

Zidovudine (Retrovir®) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies

  Zidovudine is mutagenic in 2 *in vitro* assays, clastogenic in 1 *in vitro* and 2 *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, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing 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 a middle-dose animal. No vaginal tumors were found at the lowest dose. In rats, 2 late-appearing (after 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 of 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. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

  Two transplacental carcinogenicity studies were conducted in mice *[2,3]*. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally *[3]*. The doses of zidovudine 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. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 through 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

  Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area, had no effect on fertility judged by conception rates.

  No effect of zidovudine on reproduction or fertility in rodents has been seen. 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 3,000 mg/kg/day (very near the oral median lethal 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 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 resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine 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. There were no other reported developmental anomalies. 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 (WITS), a cohort study enrolling women during pregnancy, described an association between first-trimester exposure to zidovudine and a 10-fold increased risk of hypospadius *[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. The prevalence of birth defects with first-trimester zidovudine exposure was 3.1% (95% CI: 2.5% – 3.7%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[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 67 mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine in Kenya, 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 their nursing infants, who only received zidovudine 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 antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. No difference in disease progression between women in PACTG 076 who received zidovudine and those who received placebo has been seen in follow-up through 4 years postpartum *[11]*. Infants with *in utero* zidovudine exposure followed for nearly 6 years have shown no significant differences from those who received placebo in immunologic, neurologic, and growth parameters *[6,12]*; follow-up of these infants is continuing.

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Non-Nucleoside Reverse Transcriptase Inhibitors

For information regarding potential interaction of the non-nucleoside reverse transcriptase inhibitor drug class and methergine, see **Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use**. For more information regarding nevirapine hepatic/rash toxicity, see **Nevirapine and Hepatic/Rash Toxicity**.

Delavirdine (Rescriptor®) is no longer available in the United States.

Efavirenz (Sustiva®) is classified as FDA pregnancy category D.

- Animal carcinogenicity studies
  Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies with efavirenz in mice and rats have been completed. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice but an increase in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas above background were found in female mice. In male and female rats administered systemic drug exposures lower than that in humans receiving therapeutic doses, no increase in tumor incidence above background was observed.
- Reproduction/fertility animal studies
  No effect of efavirenz on reproduction or fertility in rodents has been seen.
- Teratogenicity/developmental toxicity
  An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational Days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure) *[1]*. The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

  In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through July 2008, birth defects were observed in 13 (3.2%) of 407 (95% CI: 1.7% – 5.4%) live births with first-trimester exposure. Defects reported prospectively after first-trimester efavirenz exposure included a case of sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome and a case of bilateral facial clefts, anophthalmia, and amniotic band *[2]*. Other defects reported included polydactyly (3 cases), hydronephrosis, bilateral hip dislocation and umbilical hernia, bilateral hip dislocation, urinary obstruction with duplicated right collecting system, long bone malformation, shortening of right leg, cutis aplasia, and hip dysplasia with pulmonary stenosis. In retrospective case reports, there are 3 cases of neural tube defects in infants born to mothers receiving efavirenz during the first trimester *[3]* as well as 2 additional infants with another CNS defect (Dandy-Walker malformation). The specific cases include a report of multiple

defects, including Dandy-Walker CNS malformation in a fetus from a spontaneous abortion, a second infant with Dandy-Walker malformation, a fetus with a neural tube defect in a pregnancy with elective termination in second trimester after the defect was diagnosed, and 2 cases of myelomeningocele in infants born to women who were receiving efavirenz at the time of conception and during the first trimester *[4,5]*. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

- Placental and breast milk passage
  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery *[6]*. Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz passed into breast milk with a ratio of 0.54 (mean breast milk to mean maternal plasma concentration) and 4.08 (mean skim milk to mean newborn plasma concentration). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. No data about efavirenz in neonates are currently available.

- Human studies in pregnancy
  Limited data on use of efavirenz in pregnancy are available. In 1 study of 71 pregnancies occurring among women in a primary therapy study, the rate of early losses and stillbirths did not differ among women on efavirenz or other drugs *[7]*. Among 22 livebirths to women exposed to efavirenz in the first trimester, 1 (4.5%) infant had an abnormality, right limb shortening.

Efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz and should be counseled about the potential risk to the fetus and need to avoid pregnancy. Different types of contraception have known failure rates in women not receiving antiretroviral drugs; these failure rates may increase with drug interactions between estrogen-progesterone hormonal contraceptives and some antiretroviral drugs, including efavirenz. Alternate antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Barrier contraception should always be used in combination with other methods of contraception (e.g., hormonal contraceptives, intrauterine device). A study evaluating the interaction between efavirenz and depomedroxyprogesetrone (DMPA) in 17 women found no change in the pharmacokinetic profile of either efaviraenz or DMPA with concomitant use *[8]*. DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

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Etravirine (Intelence®, ETV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of etravirine in rodents are ongoing.
- Reproduction/fertility
  No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).
- Teratogenicity/developmental toxicity
  Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1,000 mg/kg/day). In both species, no treatment-related embryo-fetal effects including malformations were observed. In addition, no treatment effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).
- Placental and breast milk passage
  There are no data on whether etravirine crosses the placenta or is excreted in breast milk in humans.
- Human studies in pregnancy
  No adequate and well-controlled studies of etravirine use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients.

Nevirapine (Viramune®) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known.
- Reproduction/fertility
  Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.
- Teratogenicity/developmental toxicity
  Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on AUC). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to nevirapine 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 nevirapine. The prevalence of birth defects with first-trimester nevirapine exposure was 2.3% (95% CI: 1.4% – 3.6 %) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk passage
  Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *[2]*. Nevirapine is excreted into human breast milk; the median concentration in 4 breast milk samples obtained from 3 women during the first week after delivery was approximately 76% (range 54% – 104%) of serum levels *[2]*. In 19 women receiving combination therapy with nevirapine, lamivudine, and zidovudine, breast milk nevirapine concentration was 6,795 ng/mL, which was 0.67 times that of maternal serum *[3]*. In a larger study, 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine in Kenya; median nevirapine breast milk concentration was 4,564 ng/mL *[4]*. Their infants, who only received nevirapine via breast milk, had a median nevirapine concentration of 734 ng/mL.

- Human studies in pregnancy

Short-Term Peripartum Prophylaxis:

A Phase I study (PACTG 250) evaluated the safety and pharmacokinetics of nevirapine administered to infected pregnant women as a single 200-mg dose at the onset of labor and as a single 2-mg/kg dose to the infant at age 48 to 72 hours *[2]*. No adverse effects were seen in the women or the infants.

Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar although somewhat more variable than in nonpregnant adults, possibly due to incomplete drug absorption associated with impaired gastrointestinal function during labor. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

The safety, toxicity, and pharmacokinetics of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants *[5]*. Initial dose pharmacokinetic profiles in pregnant women were similar to those seen in nonpregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by Day 7 of life in 4 of 8 infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared with newborns whose mothers received only a single intrapartum nevirapine dose.

The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14 to 16 weeks of life compared with zidovudine *[6]*. However, the women in this African trial were not receiving any other antiretroviral therapy.

In the United States, most infected women who know their HIV status during pregnancy receive combination antiretroviral therapy, usually including zidovudine, as well as intravenous zidovudine during delivery, with 6 weeks of zidovudine given to their infant. A Phase III perinatal trial (PACTG 316) conducted in the United States, Europe, the Bahamas, and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard antiretroviral therapy (at minimum the PACTG 076 zidovudine regimen; 77% of women in the trial received combination therapy) would provide additional benefits in reducing transmission. Transmission was not significantly different between those who had the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[7]*.

Nevirapine resistance can be induced by a single mutation. As a result of its long half-life, nevirapine can be detected in plasma up to 3 weeks after administration of a single intrapartum dose *[8]*. This period of selective pressure of nevirapine monotherapy may predispose to the development of resistant strains of HIV *[9]*. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral-naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor *[10,11]*. The clinical implications of the presence of nevirapine-resistant HIV are unclear. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13 to 18 months postpartum *[12]*. Evaluation at later time points was not done in PACTG 316. Single-dose nevirapine appears to be as effective in preventing HIV transmission in subsequent pregnancies as when it is used for the first time *[13,14]*. Several studies have suggested that there is no decrease in efficacy when nevirapine-based combination therapy is started at least 6 to 12 months after delivery *[15-18]*. Administration of postpartum antiretrovirals to the mother can reduce the frequency of detection of nevirapine-resistant strains *[9,19-21]*.

Longer Term Antenatal Combination Therapy:

The pharmacokinetics of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination antiretroviral therapy during pregnancy. A study that determined nevirapine pharmacokinetics in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine pharmacokinetic parameters *[22]*. In contrast, in nevirapine pharmacokinetic data from a therapeutic drug monitoring program that included 12-hour sampling, nevirapine clearance was 20% greater, AUC was 28% lower, and C_{max} was 30% lower in 16 pregnant women compared to 13 nonpregnant women *[23]*.

Severe, life-threatening, and in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic

necrosis, and hepatic failure, and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual HIV exposure *[24]*. These toxicities have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women *[25-27]*. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men *[28]*. The degree of risk for hepatic toxicity varies with CD4 cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity *[28]*. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash *[26]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5% – 11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, ranging between 0.04% and 0.40% *[28,29]*. Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine *[29]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs *[30,31]*. Women initiating nevirapine with CD4 counts >250 cells/mm^3, including pregnant women receiving antiretroviral drugs solely for prevention of transmission, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal *[32]*. Nevirapine should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4 counts below 250/mm^3 can receive nevirapine-based regimens, and women who enter pregnancy on nevirapine regimens and are tolerating the regimens well may continue therapy, regardless of CD4 count. Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through 4 months, and every 1 to 3 months thereafter (**Adult Antiretroviral Guidelines**); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and then monthly *[33]*. Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or have asymptomatic but severe transaminase elevations should stop nevirapine and not receive nevirapine therapy in the future.

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Protease Inhibitors

For information regarding the protease inhibitor (PI) class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see **Protease Inhibitor Therapy and Hyperglycemia** and **Combination Antiretroviral Therapy and Pregnancy Outcome**.

Amprenavir (Agenerase®) is no longer available in the United States.

Atazanavir (Reyataz®, ATV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  In *in vitro* and *in vivo* assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 7.2-fold higher than those in humans at the recommended therapeutic dose (400 mg once daily). There were no increases in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 5.7-fold higher than those in humans at the recommended therapeutic dose.
- Reproduction/fertility
  No effect of atazanavir on reproduction or fertility in male and female rodents was seen at systemic drug exposures (AUC up to 2 times those achieved in humans at the recommended therapeutic dose).
- Teratogenicity/developmental toxicity
  Atazanavir did not produce teratogenic effects in rabbits with maternal dosing producing systemic drug exposure equivalent to (rabbits) or 2 times that (rats) achieved in humans at the recommended therapeutic dose (400 mg once daily). In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 2 times the human exposure also resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.

  In a retrospective analysis from London of atazanavir used in 31 women during 33 pregnancies (20 of whom were receiving atazanavir at conception), there were 2 miscarriages at 12 and 16 weeks, 26 infants born, and 5 women still pregnant *[1]*. No infant required phototherapy and no birth defects were seen; none of the infants were HIV infected. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to atazanavir 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 atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.0% (95% CI: 0.7% – 4.7%)

compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[2]*.

Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase enzyme occurs frequently during treatment with atazanavir. Studies have demonstrated that infants born to mothers who received atazanavir during pregnancy do not have pathologic or dangerous bilirubin elevations in the newborn period *[1,3-5]*.

- Placental and breast milk passage
  In studies of women receiving atazanavir/ritonavir-based HAART during pregnancy, cord blood atazanavir concentration averaged 13% – 16% of maternal serum levels at delivery *[3,5]*. Atazanavir is excreted in the milk of lactating rats. In a small study of 3 women, the median ratio of breast milk atazanavir concentration to that in plasma was 13% *[6]*.

- Human studies in pregnancy
  The pharmacokinetics of atazanavir 300 mg when administered once daily during pregnancy with ritonavir 100 mg have been investigated in 4 studies. In a retrospective study, trough atazanavir concentrations were measured in 19 pregnant women at a median of 30 weeks gestation (14 in third trimester); all but 2 women had a trough atazanavir concentration greater than 100 ng/mL *[1]*. Full pharmacokinetic profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy have been evaluated in 3 studies. In a study of 17 pregnant women, atazanavir AUC was not different during pregnancy compared to 1 – 6 months postpartum (28.5 ug*hr/mL vs. 30.5 ug*hr/mL, respectively) *[3]*. In contrast, Eley et al. determined atazanavir pharmacokinetics in 12 pregnant women and found reductions in atazanavir concentrations of more than 50% during pregnancy, with a mean AUC of 26.6 ug*hr/mL during the third trimester compared to 57.0 ug*hr/mL at 4 weeks postpartum. All subjects had trough atazanavir concentrations greater than 150 ng/mL *[4]*. Similarly, Mirochnick et al. described atazanavir pharmacokinetics in 18 women not receiving tenofovir, with median AUC of 41.9 ug*hr/mL during pregnancy versus 58.0 ug*hr/mL at 6 – 12 weeks postpartum *[5]*. Atazanavir AUC was further reduced in 15 women also receiving tenofovir, with median AUC of 30.5 ug*hr/mL during pregnancy compared to 44.1 ug*hr/mL postpartum. Mean atazanavir AUC in nonpregnant adults receiving 300 mg plus 100 mg ritonavir daily dosing is 57.0 ug*hr/mL and is reduced by about 25% in adults receiving concomitant tenofovir *[7,8]*. Investigations of atazanavir exposure with the use of an increased dose of 400 mg in combination with 100 mg ritonavir during pregnancy are under way.

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Darunavir (Prezista™) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Darunavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males and females of both mice and rats as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7-and 1-fold (rats) of those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).
- Reproduction/fertility
  No effects on fertility and early embryonic development were seen with darunavir in rats.
- Teratogenicity/developmental toxicity
  No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat pre- and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir during lactation due to exposure of pups to drug substances via the milk. In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5 to 11 days) or multiple doses of darunavir (40 mg/kg to 1,000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Exposures and toxicity profiles of rats with chronic exposure (30 mg/kg); however, significant bone-related toxicity has been shown in <25% of infants studied. Sexual development, fertility, or mating performance of offspring were not affected by maternal treatment. No data are available in humans.
- Placental and breast milk passage
  No animal studies of placental passage of darunavir have been reported. As noted above, passage of darunavir into breast milk has been noted in rats. It is unknown if placental or breast milk passage of darunavir occurs in humans.
- Human studies in pregnancy
  No studies of darunavir have been conducted in pregnant women or neonates. Darunavir is not recommended for children younger than 3 years.

Fosamprenavir (Lexiva™) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily.
- Reproduction/fertility
  No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No affect was seen on the development or maturation of sperm in rats at these doses.

- Teratogenicity/developmental toxicity
  Fosamprenavir was studied in rabbits at 0.8 and in rats at 2 times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at 2 times human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.
- Placental and breast milk passage
  It is unknown whether fosamprenavir crosses the placenta. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.
- Human studies in pregnancy
  There are very limited data on fosamprenavir in pregnant women. There is a pediatric liquid formulation approved for children older than 2 years, but there is no dosing information for neonates.

Indinavir (Crixivan®) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  There is no evidence that indinavir is mutagenic or clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.
- Reproduction/fertility
  No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.
- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity or treatment-related effects on embryonic/fetal survival or fetal weights of indinavir in rats, rabbits, or dogs at exposures that were comparable to humans or slightly greater. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1% – 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to indinavir 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 indinavir The prevalence of birth defects with first-trimester indinavir exposure was 2.2% (95% CI: 0.8% – 4.7%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk passage
  Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In a Phase I study in pregnant women and their infants (PACTG 358, see below), transplacental passage of indinavir was minimal *[2]*. Additionally, in a study of cord blood samples from 21 women treated with indinavir during pregnancy, the cord blood concentration of indinavir was below the assay limit of detection in samples from all women *[3]*. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26 to 1.45); it is not known if indinavir is excreted in human milk.

- Human studies in pregnancy
  The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A Phase I/II safety and pharmacokinetic study (PACTG 358) of indinavir (800 mg tid) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants was conducted *[2]*. The mean indinavir plasma $AUC_{0\text{-}8hr}$ at weeks 30 to 32 of gestation (n = 11) was 74% (95% CI: 50% – 86%) lower than that observed 6 weeks postpartum. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in nonpregnant patients in another study. In another study, 2 pregnant HIV-infected women receiving combination therapy including indinavir (800 mg tid) had significantly reduced AUC indinavir exposures in the third trimester compared to postpartum evaluations (52% and 86% respectively) *[4]*. Therefore, given the substantially lower antepartum exposures observed in these studies and the generally limited data in this patient population, use of indinavir as a sole PI is not recommended in HIV-infected pregnant patients.

  Two studies have evaluated indinavir used in conjunction with low-dose ritonavir in twice-daily dosing. The first evaluated 2 women whose regimen included indinavir 800 mg bid with ritonavir 200 mg bid. Both women achieved third-trimester AUC indinavir levels greater than those for historical nonpregnant controls *[4]*. A more recent study evaluated use of combination therapy including indinavir 400 mg bid with ritonavir 100 mg bid. Data are available for 28 women, 23 (82%) of whom had C_{trough} values above the targeted cutoff of 120 ng/mL. Of the 5 women with low C_{trough} values, 3 had undetectable HIV RNA viral loads at delivery *[5]*. Based on these data, indinavir may be used in pregnancy with ritonavir boosting. Given the limited data on appropriate dosing, HIV RNA levels and potentially trough drug levels should be monitored during use in pregnancy.

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Lopinavir + Ritonavir (Kaletra™) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on AUC_{0-24hr} measurement). Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.
- Reproduction/fertility
  Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.
- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity with administration of lopinavir + ritonavir to pregnant rats or rabbits. In rats treated with maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of

the exposures in humans at the recommended therapeutic dose. In a peri- and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposures of 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lopinavir + ritonavir 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 lopinavir + ritonavir. The prevalence of birth defects with first-trimester lopinavir + ritonavir exposure was 1.9% (95% CI: 0.8% – 3.7%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Lopinavir crosses the human placenta; in a pharmacokinetic study, P1026s, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20 +/- 0.13. For ritonavir, data in humans indicate only minimal transplacental passage (see Ritonavir). Lopinavir and ritonavir are secreted in the breast milk of lactating rats; it is not known if either drug is excreted in human milk.

- Human studies in pregnancy
  The capsule formulation of lopinavir/ritonavir is no longer available; it has been replaced by a new tablet formulation of lopinavir 200 mg/ritonavir 50 mg that is heat stable and does not have a food requirement.

  In nonpregnant adults, plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg lopinavir/ritonavir tablets are similar to those achieved with three 133/33 mg lopinavir/ritonavir capsules given with food, but with less pharmacokinetic variability. In a study of 51 pregnant women, plasma trough lopinavir levels during the third trimester were compared among 28 women receiving the capsule and 23 women receiving the tablet formulations at standard dosing. No statistical difference was found between the group, with a mean lopinavir trough level of 4.86 mg/L (capsule) and 4.57 mg/L (tablets) *[2]*. However, the inter-individual variability was lower with the tablets than the capsules. Five of 28 women (17.8%) in the capsule group and 4 of the 23 women (17.4%) in the tablet group had trough levels below the target (3 mg/L); 7 of the 9 women had HIV RNA levels below detection at the time of their sampling, and 2 with subtherapuetic levels (0.7 and 2.44 mg/L) had plasma RNA of 83 and 56 copies/mL, respectively, at time of their sampling.

  P1026s evaluated lopinavir pharmacokinetics following standard dosing with the new lopinavir/ritonavir tablet formulation (2 tablets twice daily) until 30 weeks gestation, followed by an increase to 3 tablets twice daily and return to standard dosing at postpartum hospital discharge. Median AUC was 72 µg*h/mL in 7 women receiving standard dosing during the second trimester, 97 µg*h/mL in 25 women receiving the increased dose during the third trimester, and 129 µg*h/mL in 19 women receiving standard dosing at 2 weeks postpartum. These data suggest that the higher lopinavir/ritonavir dose should be used in third-trimester pregnant women and that it should be considered in second-trimester pregnant women, especially those who are PI experienced, and that lopinavir/ritonavir can be reduced to standard dosing shortly after delivery *[3]*.

  Once-daily dosing of lopinavir/ritonavir capsules or tablets is not recommended in pregnancy because there are no data to address whether drug levels are adequate with such administration.

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Nelfinavir (Viracept®) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Nelfinvair was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, thyroid follicular cell adenomas and carcinomas were increased over baseline in male rats receiving 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1,000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses) of nelfinavir.
- Reproduction/fertility
  No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure. Additional studies in rats indicated that exposure to nelfinavir in females from midpregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir.
- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to humans and in rabbits with exposures significantly less than humans.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nelfinavir 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 nelfinavir. The prevalence of birth defects with first-trimester nelfinavir exposure was 3.5% (95% CI: 2.5% – 4.8%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk transfer
  In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal *[2]*. Additionally, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was below the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 ug/mL) in the remaining 14 women *[3]*. Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.
- Human studies in pregnancy
  A Phase I/II safety and pharmacokinetic study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants was conducted *[2]*. Nelfinavir administered at a dose of 750 mg tid produced drug exposures in the first nine pregnant HIV-infected women enrolled in the study that were variable and generally lower than those reported in nonpregnant adults for both tid and bid dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1,250 mg twice daily), which resulted in adequate levels of nelfinavir in pregnancy. However, in another study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in their second trimester and lower concentration than in nonpregnant women *[4]*.

  In a pharmacokinetic study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1,250 mg twice daily) in 25 women at 30 to 36 weeks gestation (and 12 also at 6 to 12 weeks postpartum), peak levels and AUC were lower in the third trimester than postpartum *[5]*. Only 16% (4/25) of women during third trimester and 8% (1/12) women postpartum had trough values above the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in third trimester and 86% postpartum.

  In September 2007, the manufacturer of nelfinavir (Viracept) in the United States (Pfizer) sent a letter to providers regarding the presence of low levels of ethyl methane sulfonate (EMS), a process-related impurity, in nelfinavir. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data from humans exists and no increase in birth defects has been observed in the Antiretroviral Pregnancy Registry. Health care providers were advised not to initiate antiretroviral regimens containing Viracept (nelfinavir) in their pregnant female or new pediatric patients and to switch pregnant patients receiving Viracept (nelfinavir) to alternative therapy unless no alternative was available. As of March 31, 2008, all Viracept (nelfinavir) manufactured and released by Pfizer now meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients. Viracept (nelfinavir) may now be prescribed for pregnant women as an alternate PI for women receiving antiretroviral therapy during pregnancy solely for prevention of MTCT.

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Ritonavir (Norvir®) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, at levels of 50, 100, or 200 mg/kg/day, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed; based on AUC, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of the human exposure at the recommended therapeutic dose.
- Reproduction/fertility
  No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible due to hepatic toxicity in the rodents.
- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity was observed in rats, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with ritonavir. The prevalence of birth defects with first-trimester ritonavir exposure was 2.3% (95% CI: 1.4% – 3.6%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk transfer
  Transplacental passage of ritonavir has been observed in rats with fetal tissue to maternal serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue *[2]*. In a Phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal *[3]*. Additionally, in a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was below the assay limit of detection in 83%, and was only 0.38 ug/mL in the remaining woman *[4]*. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.
- Human studies in pregnancy
  A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy compared to postpartum *[3]*.

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Saquinavir (Invirase® [Hard Gel Capsule]) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Saquinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years, at plasma exposures approximately 60% of those obtained in humans at the recommended therapeutic dose (rats) and at exposures equivalent to those in humans at the recommended therapeutic dose (mice).
- Reproduction/fertility
  No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.
- Teratogenicity/developmental toxicity
  No evidence for embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.
- Placental and breast milk transfer
  Placental transfer of saquinavir in the rat and rabbit was minimal. In a Phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal *[1]*. Additionally, in a study of cord blood samples from eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was below the assay limit of detection in samples from all women *[2]*. Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.
- Human studies in pregnancy
  Three studies have evaluated the pharmacokinetics of saquinavir-hard gel capsules (HGC) combined with low-dose ritonavir (saquinavir-HGC 1,000 mg/ritonavir 100 mg given twice daily) in a total of 19 pregnant women; trough levels were greater than the target in all but 1 woman *[3,4]*. In a small study of 2 women who received saquinavir-HGC 1,200 mg/ritonavir 100 mg given once daily, trough levels were 285 and 684 ng/mL and the $AUC_{0\text{-}24}$ were 28,010 and 16,790 ng hour/mL, greater than the target AUC of 10,000 ng hour/mL *[5]*. Thus, the limited available data suggest that saquinavir-HGC 1,000 mg/ritonavir 100 mg given twice daily should achieve adequate trough levels in HIV-infected pregnant women. Data are too limited to recommend once-daily dosing at present. However, a recent analysis of saquinavir-HGC administered once daily at 1,200mg/100mg ritonavir combined with various NRTIs during 46 pregnancies, demonstrated saquinavir levels greater than the target C_{min} in 46 (93.4%) of pregnancy episodes and undetectable viral load at delivery in 88% of episodes *[6]*. Target levels were achieved in the other 3 women with a dose of 1,600mg/100mg. The drug was well tolerated.

  The pharmacokinetics of the new 500-mg tablet formulation of saquinavir boosted with ritonavir in a dose of saquinavir 1,000 mg/ritonavir 100 mg given twice daily was studied in 14 HIV-infected pregnant women at 33 weeks gestation and parameters were comparable to those observed in nonpregnant individuals; none of the women had a subtherapeutic trough level *[7]*.

  One study of saquinavir/ritonavir-based HAART in 42 women during pregnancy reported abnormal transaminase levels in 13

women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity grade 1 – 2 in most, 1 woman had grade 3) *[8]*.

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Tipranavir (Aptivus®) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Tipranavir was neither mutagenic nor clastogenic in a battery of five *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except the low dose of tipranavir. These tumors were also increased in male mice at the high dose of tipranavir and the tipranavir/ritonavir combination group. Hepatocellular carcinoma incidence was increased in female mice given the high dose of tipranavir and both sexes receiving tipranavir/ritonavir. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on AUC or C_{max}) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100, or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day tipranavir/ritonavir in combination, or 10 mg/kg/day ritonavir. No drug-related findings in male rats were observed. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.
- Reproduction/fertility
  Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels similar to human exposures at the recommended clinical dose (500/200 mg per day of tipranavir/ritonavir).
- Teratogenicity/developmental toxicity
  No teratogenicity was detected in studies of pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold

human exposure. In rats exposed to 400 mg/kg/day (~0.8-fold human exposure) and above, fetal toxicity (decreased ossification and body weights) was observed. Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold exposures in humans. In rats, no adverse effects were seen on development at levels of 40 mg/kg/day (~0.2-fold human exposure), but growth inhibition in pups and maternal toxicity were seen at 400 mg/kg/day (~0.8-fold human exposure).

- Placental and breast milk transfer
  No animal studies of placental or breast milk passage of tipranavir have been reported. It is unknown if placental or breast milk passage of tipranavir occurs in humans.
- Human studies in pregnancy
  No studies of tipranavir have been conducted in pregnant women or neonates.

ENTRY INHIBITORS

Two drugs have been approved in this new class of antiretrovirals aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein gp120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor (e.g., CCR5 or CXCR4) on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the "fusion peptide" of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a "zipping" together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous administration, is a synthetic 36 amino acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41, and the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other antiretroviral drugs to treat advanced HIV infection in adults and children aged 6 years or older. Maraviroc interferes with viral entry at the chemokine coreceptor level; it is a CCR5 coreceptor antagonist approved for combination therapy of HIV infection in adults infected with CCR5-tropic virus.

Enfuvirtide (Fuzeon™, T-20) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Enfuvirtide was neither mutagenic or clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.
- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a m^2 basis).
- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.2 times, respectively, the adult human daily dose on a m^2 basis.
- Placental and breast milk passage
  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or radio-labeled metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide crosses the human placenta or is excreted in human milk. A published case report of two peripartum pregnant patients and their neonates and data from an *ex vivo* human placental cotyledon perfusion model suggest that enfuvirtide does not cross the placenta *[1,2]*.
- Human studies in pregnancy
  Very limited data exist on the use of enfuvirtide in pregnant women *[1,3,4]*; no data exist in neonates.

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Maraviroc (Selzentry®) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies found no increase in tumor incidence in mice (transgenic rasH2 mice) and rats at exposures up to 11-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats. Maraviroc produced no adverse effects on fertility of male or female rats or sperm of male rats at exposures up to 20-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from maraviroc administered in doses up to 20-fold higher in rats and 5-fold higher in rabbits than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Placental and breast milk passage
  It is unknown if maraviroc crosses the placenta in animals or humans. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.
- Human studies in pregnancy
  No studies of maraviroc have been conducted in pregnant women or neonates.
- Additional concerns
  Although no increase in malignancy has been observed, maraviroc has a potential for an increased risk of malignancy due to the drug's mechanism of action and possible effects on immune surveillance.

INTEGRASE INHIBITORS

One drug has been approved in this new class of antiretrovirals aimed at inhibiting the viral enzyme integrase, the viral enzyme catalyzing the two-step process of insertion of HIV DNA into the genome of the host cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA, and a final "strand transfer" step that inserts the viral DNA into the exposed regions of cellular DNA. This second step of the integration process is targeted by the integrase inhibitor drug class. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects retrotranscription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV resistant to other classes of antiretroviral drugs.

Raltegravir (Isentress™) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of raltegravir are ongoing.
- Reproduction/fertility animal studies
  Raltegravir produced no adverse effects on fertility of male or female rats at doses up to 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended adult human dose).

- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses producing systemic exposures approximately 3- to 4-fold higher than the exposure at the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended human daily dose).
- Placental and breast milk passage
  Placental transfer of raltegravir was demonstrated in both rats and rabbits. In rats given a maternal dose of 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5- to 2.5-fold higher than in maternal plasma at 1 and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentrations in fetal plasma were approximately 2% of the mean maternal plasma concentration at both 1 and 24 hours following a maternal dose of 1,000 mg/kg/day. Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. There were no effects in rat offspring attributable to raltegravir exposure through breast milk.
- Human studies in pregnancy
  No studies of raltegravir have been conducted in pregnant women or neonates. It is unknown if raltegravir is secreted in human milk.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry is an epidemiologic project to collect observational, nonexperimental data on antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.

It is strongly recommended that health care providers who are treating HIV-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry does not use patient names, and birth outcome follow-up is obtained by registry staff from the reporting physician.

Referrals should be directed to:
Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1–800–258–4263
Fax: 1–800–800–1052
Internet access www.APRegistry.com.