Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

There are currently seven approved nucleoside analogue reverse transcriptase inhibitors. Data are available from clinical trials in human pregnancy for zidovudine, abacavir, lamivudine, didanosine**,** and stavudine. Emtricitabine, and zalcitabine have not been studied in pregnant women. 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 text, **Mitochondrial Toxicity and NRTI Drugs**.

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

- Animal carcinogenicity studies
  Some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive. 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).

- 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 3.2% (95% CI: 1.7% – 5.4%) 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.

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

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies in rodents given didanosine have been negative.

- Reproduction/fertility
  There has been no effect of didanosine on reproduction or fertility in rodents or on preimplantation mouse embryos *[3]*.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity or toxicity was observed with

administration of high doses of didanosine to pregnant rats, mice, or rabbits. Among cases of first trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 5.8% (15/259). 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 (cord-to-maternal blood ratio, 0.35 – 0.11) *[4]*. Didanosine is excreted in the milk of lactating rats; 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 *[4]*. 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 *[5-7]*; 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 text, **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.

Emtricitabine (Emtriva®, FTC) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test) or the mouse lymphoma or mouse micronucleus assays. 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 area under the curve) 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.

- 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 *[8]*. It is unknown if emtricitabine crosses the placenta in humans or is excreted in human milk.

- Human studies in pregnancy
  There have been no studies of emtricitabine in pregnant women or neonates.

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

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies in rodents administered lamivudine have been negative.

- Reproduction/fertility
  There appears to be no effect of lamivudine on reproduction or fertility in rodents.

- Teratogenicity/developmental toxicity studies
  There is no evidence of lamivudine-induced teratogenicity. Early embryolethality was seen in rabbits but not in rats at doses similar to human therapeutic exposure.

  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: 2.2% – 3.8%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal

concentrations *[9]*. Lamivudine is excreted into human breast milk.

- 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 *[9]*. 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 to 6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is not known.

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

- Animal carcinogenicity studies
  Some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive. 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 *[3]*.

- Teratogenicity/developmental toxicity studies
  No evidence of teratogenicity of stavudine has been observed in pregnant rats and rabbits. Developmental toxicity, consisting of a small increase in neonatal mortality and minor skeletal ossification delay, occurred at the highest dose in rats.

  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 2.8% (95% CI 1.3% – 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 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 *[10]*. 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 *[11]*. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of stavudine *[12]*.

  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 *[5-7]*; 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 text, **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.

Tenofovir disoproxil fumarate [DF] (Viread™) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out. 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
  Reproductive toxicity has been evaluated in rats and rabbits. Tenofovir had no adverse effects on fertility or

general reproductive performance in rats at doses up to 600 mg/kg/day (exposure equivalent to approximately 10 times the human dose based on body surface area comparisons). However, there was an alteration of the estrous cycle in female rats administered 600 mg/kg/day of tenofovir.

- Teratogenicity/developmental toxicity
  No adverse effects on embryo/fetal development were seen when tenofovir was given in doses up to 450 mg/kg/day to pregnant rats and 300 mg/kg/day to pregnant rabbits. When tenofovir was administered to pregnant rats in doses of 450–600 mg/kg/day, which are maternally toxic doses, peri- and post-natal development studies of their offspring showed reduced survival and slight delay in sexual maturation. However, there were no adverse effects on growth, development, behavior, or reproductive parameters when tenofovir was administered to pregnant rodents at doses that were not associated with maternal toxicity (150 mg/kg/day). 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 *[13]*. 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 2.6% 95% CI: 1.1% – 5.4%) 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
  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 *[14]*. In 2 studies including 21 pregnant women receiving tenofovir-based therapy, the cord-to-maternal blood ratio ranged from 0.95 to 0.99 *[15, 16]*. 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 highly active antiretroviral therapy (HAART) in study P1026s at 30 to 36 weeks gestation and 6 to 12 weeks postpartum *[15]*. 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.

Zalcitabine (HIVID®, ddC) is classified as FDA pregnancy category C. *(no longer available in the United States)*

- Animal carcinogenicity studies
  High doses of zalcitabine (more than 1,000 times that of human therapeutic exposure) have been associated with the development of thymic lymphomas in rodents.

- Reproduction/fertility
  No effect of zalcitabine on reproduction or fertility in rodents has been seen. However, there is a dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition at a zalcitabine concentration of 100 μM; no inhibition of postblastocyst development was observed *[3]*.

- Teratogenicity/developmental toxicity
  Teratogenicity (hydrocephalus) occurred in rats given very high doses (more than 1,000 times the maximally recommended human exposure) of zalcitabine.

Developmental toxicity, consisting of decreased fetal weight and skeletal defects, has been seen in rodents at moderate to high zalcitabine doses. Cytotoxic effects were observed on rat fetal thymocytes at zalcitabine concentrations as low as 10 μM (approximately 100 times human therapeutic exposure).

- Placental and breast milk passage
  In primate and placental perfusion studies, zalcitabine crosses the placenta (fetal-to-maternal drug ratio approximately 0.50 to 0.60) *[17]*. In rodents, zalcitabine concentrates in the fetal kidney and a relatively small proportion (approximately 20%) reaches the fetal brain. It is unknown if zalcitabine is excreted in breast milk.

- Human studies in pregnancy
  No studies of zalcitabine have been conducted in pregnant women or neonates.

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

- Animal carcinogenicity studies
  Prolonged, continuous, high-dose zidovudine administration to adult rodents is associated with the development of nonmetastasizing vaginal squamous tumors in 13% of female rodents (at estimated drug concentrations 3 and 24 times that of human therapeutic exposure in mice and rats, respectively) *[18]*. In rodents, unmetabolized zidovudine is concentrated in urine with reflux into the vaginal vault. Therefore, vaginal tumors could be a topical effect of chronic zidovudine exposure on the vaginal mucosa. That vaginal squamous cell carcinomas were observed in rodents exposed to 20 mg/mL zidovudine intravaginally is consistent with this hypothesis *[18]*. In humans, only metabolized zidovudine is excreted in the urine. No increase in tumors in other organ sites has been seen in adult rodent studies.

  Two transplacental carcinogenicity studies of zidovudine were conducted in mice, with differing results. In one study, two very high daily doses of zidovudine were administered during the last third of gestation in mice *[19]*. These doses were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose given to humans (although the cumulative dose was similar to the cumulative dose received by a pregnant woman taking 6 months of zidovudine). In the offspring of zidovudine-exposed pregnant mice at the highest dose level followed for 12 months, a statistically significant increase in lung, liver, and female reproductive organ tumors was observed; the investigators also documented incorporation of zidovudine into the DNA of a variety of newborn mouse tissues, although this did not clearly correlate with the presence of tumors. In the second study, pregnant mice were given one of several regimens of zidovudine, at doses intended to achieve blood levels approximately 3-fold higher than human therapeutic exposure *[20]*. The daily doses received by the mice during gestation ranged from one-twelfth to one-fiftieth the daily doses received in the previous study. Some of the offspring also received zidovudine for varying periods of time over their lifespan. No increase in the incidence of tumors was observed in the offspring of these mice, except among those that received additional lifetime zidovudine exposure, in which vaginal tumors were again noted.

  Transplacental carcinogenicity studies have not been performed for any of the other available antiretroviral drugs or combinations of drugs. In January 1997, the National Institutes of Health convened an expert panel to review these animal data *[21]*. The panel concluded that the known benefit of zidovudine in reducing vertical transmission of HIV by nearly 70% (7.2 versus 21.9% with placebo) *[22]* far outweighs the theoretical risks of transplacental carcinogenicity. The panel also concluded that infants with *in utero* exposure to zidovudine (or any other antiretroviral) should have long-term follow-up for potential adverse effects. No tumors have been observed in 727 children with *in utero* zidovudine exposure followed for more than 1,100 person-years *[23]*. While these data are reassuring, follow-up is still limited and needs to be continued into adulthood before it can be concluded that there is no carcinogenic risk.

- Reproduction/fertility
  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 *[24]*.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity or toxicity was observed with administration of doses up to 500 to 600 mg/kg/day of zidovudine to pregnant rats, mice, or rabbits. However, marked maternal toxicity and an increase in fetal malformations were noted in rats given a zidovudine dose of 3,000 mg/kg/day (near the lethal dose, and 350 times the peak human plasma concentration).

  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 *[22, 25]*. 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, 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: 2.3% – 4.1%) 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
  Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. Zidovudine is excreted into human 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 *[22, 26]*. 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 *[27]*. 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 *[25, 28]*; follow-up of these infants is continuing.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Postpartum Hemorrhage, Non-Nucleoside Reverse Transcriptase Inhibitors, and Methergine Use

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

Delavirdine (Rescriptor®) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. In rats, delavirdine was noncarcinogenic at all doses studied. In mice, delavirdine was associated with an increase in hepatocellular adenoma and carcinoma in both males and females and urinary bladder tumors in males at systemic exposures 0.5- to 3-fold higher than human exposure at therapeutic doses for female mice and at exposures 0.2- to 4-fold higher in male mice.

- Reproduction/fertility
  Delavirdine does not impair fertility in rodents.

- Teratogenicity/developmental toxicity animal studies
  Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg/day during organogenesis caused ventricular septal defects. Exposure of rats to doses approximately 5 times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

  Abortions, embryotoxicity, and maternal toxicity were observed in rabbits at doses approximately 6 times human therapeutic exposure.

- Placental and breast milk passage
  Whether delavirdine crosses the placenta is unknown. Delavirdine is excreted in the milk of lactating rats; however, it is unknown if the drug is excreted in human breast milk.

- Human studies in pregnancy
  Delavirdine has not been evaluated in HIV-infected pregnant women. In premarketing clinical studies, the outcomes of seven unplanned pregnancies were reported: three resulted in ectopic pregnancies, three resulted in healthy live births, and one infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of pregnancy.

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

- Animal carcinogenicity studies
  In vitro genetic screening tests are negative for mutagenic or clastogenic effects of drug exposure. 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 rats administered systemic drug exposures lower than that in humans receiving therapeutic doses, no increase in tumor incidence above background was observed in male or female rats.

- Reproduction/fertility animal studies
  No effect of efavirenz on reproduction or fertility in rodents has been seen. An increase in fetal resorptions has been observed in rats at doses comparable to or lower than those used to achieve human therapeutic exposure.

- Teratogenicity/developmental toxicity animal studies
  Significant 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) *[29]*. The malformations included anencephaly and unilateral anophthalmia in one,

microphthalmia in another, and cleft palate in the third. Primate teratogenicity studies have not been conducted for the other non-nucleoside reverse transcription inhibitors, delavirdine or nevirapine.

- Placental and breast milk passage in animal studies
  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. It is unknown whether efavirenz is excreted in human breast milk.

- Human studies in pregnancy
  No clinical trials with efavirenz in pregnant humans are planned. Efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through January 2007, birth defects were observed in 7 of 281 live births with first trimester exposure; none of the defects in the prospective report were neural tube defects (they included polydactyly, hydronephrosis, 2 cases of bilateral hip dislocation accompanied in 1 case by umbilical hernia, and urinary obstruction secondary to duplicated right collecting system) *[1]*. However, in retrospective case reports, there are 3 cases of neural tube defects in infants born to mothers receiving efavirenz during the first trimester *[30]*, as well as an additional infant 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 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 *[31, 32]*. 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 (see teratogenicity/developmental toxicity in animal studies).

  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., oral hormonal contraceptives). There are insufficient data on drug interactions with injectable hormones (depo-provera) to make recommendations regarding the need for additional contraception. Theoretically, because hormone levels are much higher with injectable than oral contraceptives, interactions with antiretroviral drugs may be less significant.

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

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. 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.

- 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. 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 2.4% (95% CI: 1.3% – 4.1%) 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) *[33]*. Nevirapine is excreted into human breast milk; the median concentration in four breast milk samples obtained from three women during the first week after delivery was approximately 76% (range 54 to 104%) of serum levels *[33]*.

- Human studies in pregnancy
  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 *[33]*. No adverse effects were seen in the women or the infants.

Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar though 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 *[34]*. 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 *[35]*. 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 having the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[36]*. Nevirapine resistance can be induced by a single mutation. 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 *[37, 38]*. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13 to 18 months postpartum *[39]*. Evaluation at later time points was not done in PACTG 316.

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 *[40]*. 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 *[41-43]*. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men *[44]*. 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 *[44]*. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash *[42]*. 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% – 0.40% *[44, 45]*. Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine *[45]*.

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 *[46, 47]*. 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 *[48]*. 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 *[49]*. 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.

PROTEASE INHIBITORS

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

Amprenavir (Agenerase®) is classified as FDA pregnancy category C. *(no longer available in the United States)*

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. An increase in benign hepatocellular adenomas and hepatocellular carcinomas was observed in male mice and rats at the highest doses evaluated, which produced systemic exposures in mice 2-fold and in rats 4-fold higher than systemic exposure in humans receiving therapeutic doses of amprenavir. Female mice and rats were not affected.

- Reproduction/fertility
  No effect has been seen on reproductive performance, fertility, or embryo survival in rats at exposures about twice those of human therapeutic exposure.

- Teratogenicity/developmental toxicity
  In pregnant rabbits, administration of amprenavir resulting in systemic exposures about one-twentieth of that observed with human therapeutic exposure was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. In rat fetuses, thymic elongation and incomplete ossification of bones were also attributed to amprenavir at systemic exposures about one-half that associated with the recommended human dose. Reduced body weights of approximately 10% – 20% were observed in offspring of rodents administered amprenavir from Day 7 of gestation to Day 22 of lactation (exposures approximately twice that observed with the human therapeutic dose). However, the subsequent development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of amprenavir.

- Placental and breast milk passage
  Whether amprenavir crosses the placenta is unknown. 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 have been limited studies of amprenavir in pregnant women and no studies in neonates. Amprenavir oral solution contains high levels of excipient propylene glycol in the oral solution vehicle; this is not true for the capsular formulation. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Thus, while the capsule formulation of amprenavir may be used in pregnancy, amprenavir oral solution is contraindicated in pregnant women and infants and in children under the age of 4 years.

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

- Animal carcinogenicity studies
  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. 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 (as measured by area under the curve) up to two 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 equal to (rabbits) or twice that (rats) achieved in humans at the recommended therapeutic dose. In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure twice that achieved in humans at the recommended therapeutic dose 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.

  Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase enzyme occurs frequently during treatment with atazanavir. It is unknown whether treatment during pregnancy will exacerbate physiologic hyperbilirubinemia in the neonate.

- Placental and breast milk passage
  In one study of nine patients receiving atazanavir/ritonavir-based HAART during pregnancy, cord blood atazanavir concentration was only 10% of maternal serum levels *[50]*. Atazanavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  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 *[51]*. No infant required phototherapy and no birth defects were seen; none of the infants were HIV infected. Fifteen women had drug levels measured at a median of 30 weeks gestation (14 in third trimester), and all but one woman had mean trough atazanavir concentration above the recommended therapeutic concentration of 100 mg/L. In a second study, pharmacokinetic profiles were performed in 9 women at 30 to 36 weeks gestation and 8 to 16 weeks postpartum who were receiving ritonavir-boosted atazanavir-based HAART *[50]*. Large interpatient variability was seen but concentrations obtained in late pregnancy were similar to those obtained postpartum. None of the infants required phototherapy and none was HIV infected.

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

- Animal carcinogenicity studies
  Long-term carcinogenicity studies in rodents have not been completed. Darunavir tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes. Darunavir did not induce chromosomal damage in the micronucleus test in mice.

- 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. 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.

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

- Animal carcinogenicity studies
  Carcinogenicity studies of fosamprenavir in rats and mice are in progress. Results of studies with amprenavir showed an increase in the incidence of benign hepatocellular adenomas and the combined incidence of benign hepatocellular adenomas and carcinoma in males in both species at the highest doses tested, approximately 2 to 4 times the human exposure. Female mice and rats were not affected. No other benign or malignant neoplasms were increased. Fosamprenavir and amprenavir were not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays.

- 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. At these doses, the incidence of abortion was increased in rabbits, but no embryo-fetal effects were seen. 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 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. Fosamprenavir 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 over age 2 years, but no dosing information for neonates.

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

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (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 of indinavir in rats, rabbits, or dogs. 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, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 2% 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 above 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.

- 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 *[52]*. 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 *[53]*. Indinavir is excreted in the milk of lactating rats at concentrations slightly above 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 (the infants did not receive indinavir in this study). Data are available from 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment *[52]*. The mean indinavir plasma $AUC_{0\text{-}8hr}$ at weeks 30 to 32 of gestation (n = 11) was 9,231 nM*hr, which is 74% (95% CI: 50% – 86%) lower than that observed 6 weeks postpartum. Six of these 11 (55%) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. 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 pharmacokinetic study of 2 pregnant HIV-infected women receiving combination therapy including indinavir (800 mg tid), a marked difference was noted between the AUC indinavir exposure between the third trimester and postpartum evaluations *[54]*. The AUC during the third trimester was reduced by 63% in one and 86% in the other woman when compared to 9 to 12 week postpartum evaluations in the same women. Similar reductions in maximum plasma indinavir concentrations were observed. 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 protease inhibitor is not recommended in HIV-infected pregnant patients; data are not yet available regarding the pharmacokinetics of indinavir with low dose ritonavir boosting in pregnant women.

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

- Animal carcinogenicity studies
  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 (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 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 2.6% (95% CI: 1.0% – 5.6%) 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
  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. However, pharmacokinetic data on lopinavir in pregnancy are currently available only for the capsule formulation, although studies of the tablet formulation in pregnant women are under way.

  The pharmacokinetics of lopinavir/ritonavir capsules were evaluated in the second and third trimester of pregnancy in protocol P1026s. At standard adult capsule doses (3 lopinavir 133 mg/ritonavir 33 mg capsules twice daily), lopinavir levels during the third trimester were significantly lower compared to postpartum levels and those in nonpregnant adults *[55]*. Only 3 of 17 (18%) women evaluated during the third trimester had lopinavir AUC concentrations above the 10th percentile for non-pregnant adults, and none exceeded the 50th percentile; in contrast, 79% of these women evaluated postpartum had AUC values above the 10th percentile. As with ritonavir, placental passage of lopinavir was limited.

  Increasing the dose of lopinavir/ritonavir in the third trimester to 4 capsules twice daily provided adequate lopinavir exposure during the third trimester, but resulted in higher levels by 2 weeks postpartum *[56]*. However, a separate study in London of 16 pregnant HIV-infected primarily antiretroviral-naïve women receiving standard dosing of lopinavir/ritonavir capsules throughout pregnancy found that the median trough level of lopinavir in the third trimester was 3,660 ng/mL and that 94% had trough levels >1,000 ng/mL (the minimum trough required to inhibit wild-type HIV); 14 of 16 (88%) of women had virologic suppression *[57]*. Data for AUC were not provided, so these data are not comparable with P1026s data. These investigators suggested therapeutic drug monitoring during the third trimester to determine if an increased dose would be required for the capsule formulation.

  The tablet is the currently available formulation of lopinavir/ritonavir. Plasma concentrations of lopinavir

and ritonavir after administration of two 200/50 mg lopinavir/ritonavir tablets in nonpregnant patients are similar to those achieved with 3 lopinavir 133 mg/ritonavir 33 mg capsules given with food, but with less pharmacokinetic variability. In a study of 36 pregnant women, trough plasma lopinavir levels were measured during the second trimester in 23 women and third trimester in 19 women; trough levels were adequate with standard dosing (400 mg/100 mg twice daily) of the tablet formulation *[58]*. Three women had trough levels below the target but were noted to have had adherence problems.

P1026s is currently evaluating standard dosing of the new lopinavir/ritonavir tablet formulation (2 tablets twice daily) until 30 weeks gestation, followed by an increase to 3 tablets twice daily until postpartum hospital discharge, when return to standard dosing occurs. However, no data are yet available on the tablet formulation to confirm if an increased dose will be required in late pregnancy or on the safety of increased dosing, and therefore no specific recommendations can be made until further data are available.

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

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

- Animal carcinogenicity studies
  Nelfinavir is negative for mutagenicity and clastogenicity in *in vitro* and *in vivo* 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.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats and rabbits. Developmental toxicity, consisting of small increase in neonatal mortality and minor skeletal ossification delay, occurred at the highest dose in rats. 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 3.8% (95% CI: 2.4% – 5.6%) 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
  In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal *[59]*. 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 *[53]*. 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 *[59]*. 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), 1250 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 than in nonpregnant women *[60]*.

  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 *[61]*. 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 maternal-to-child transmission.

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

- Animal carcinogenicity studies
  In vitro mutagenicity and clastogenicity screening tests are negative for ritonavir. 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 liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately 4-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 9-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans 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).

  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 3.1% (95% CI: 1.4% – 5.8%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[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 *[62]*. In a Phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal *[63]*. 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 *u*g/mL in the remaining woman *[53]*. 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 *[63]*. Preliminary data indicate minimal, if any, placental passage of ritonavir.

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

- Animal carcinogenicity studies
  In vitro screening tests have been negative. 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. Administration of low doses of saquinavir to newborn rats was associated with gastrointestinal toxicity, including inflammation at the rectoanal junction and red anal fluid; mortality was seen at very high doses (1,200 mg/kg/day).

- Teratogenicity/developmental toxicity
  No evidence for embryotoxicity or teratogenicity of saquinavir has been found in animal studies.

- 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 *[64]*. 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 *[53]*. Saquinavir 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 386) of saquinavir-soft gel capsule (SGC) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants was conducted. The standard adult dose of saquinavir (1,200 mg tid) as a single protease inhibitor was not sufficient to produce adequate drug levels in the first four pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in nonpregnant adults. Thus, the study was modified to evaluate the combination of saquinavir-SGC (800 mg) plus ritonavir (100 mg), both administered twice daily. This regimen was well tolerated and achieved adequate saquinavir levels in the women *[64, 65]*. However, saquinavir-SGC is no longer manufactured, as the saquinavir-hard gel capsule (HGC) is better tolerated and requires fewer daily capsules.

Three studies evaluated the pharmacokinetics of saquinavir-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 above the target in all but 1 woman *[66, 67]*. 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, above the target AUC of 10,000 ng*hour/mL *[68]*. 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.

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 *[69]*.

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) *[70]*.

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

- Animal carcinogenicity studies
  Long-term carcinogenicity bioassays are currently in progress. Tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five tests including the Ames bacterial reverse mutation assay, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

- Reproduction/fertility
  Tipranavir had no effect on fertility or early embryonic development in rats at dose levels similar to human exposures.

- 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
  Long-term animal carcinogenicity studies of enfuvirtide have not been conducted. Enfuvirtide was neither mutagenic or clastogenic in a series of *in vitro* and animal *in vivo* screening tests.

- 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 3.7 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 from 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. In an *ex vivo* human placental cotyledon perfusion model, enfuvirtide did not cross the placenta *[71]*.

- Human studies in pregnancy
  Very limited data exist on the use of enfuvirtide in pregnant women *[72]*; no data exist in neonates.

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 and rats at exposures up to 11-fold higher than experienced with human therapeutic exposure.

- 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.

- 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.

- 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
  Long-term animal carcinogenicity studies of raltegravir are ongoing. Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests.

- 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.

- 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.

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