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



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## Protease Inhibitors

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

Ten protease inhibitors (PIs) are currently approved (amprenavir is no longer available in the United States). Data are available from clinical trials in human pregnancy for atazanavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir. Data in pregnancy are limited for darunavir, fosamprenavir, and indinavir. Very limited data in pregnancy are available for tipranavir.

For information regarding the 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 in the perinatal guidelines.

***Amprenavir (Agenerase, APV)*** is no longer available in the United States.
**(Last updated September 14, 2011; last reviewed July 31, 2012)**

***Atazanavir (Reyataz, ATV)*** is classified as Food and Drug Administration (FDA) Pregnancy Category B.
**(Last updated July 31, 2012; last reviewed July 31, 2012)**

- 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 2.8- to 2.9-fold higher than those in humans at the recommended therapeutic dose (300 mg/day atazanavir boosted with 100 mg/kg/day ritonavir). 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 1.1-fold (males) or 3.9-fold (females) 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. The area under the curve (AUC) at this exposure level in rats was 0.9-fold in males and 2.3-fold in females compared with the exposures achieved in humans at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals at systemic drug exposure levels (AUC) 0.7 (in rabbits) to 1.2 (in rats) times those observed at the human clinical dose (300 mg/day atazanavir boosted with 100 mg/day ritonavir). In developmental toxicity

studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 1.3 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 was 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 1.9% (13 of 669 births; 95% confidence interval [CI], 1.0%–3.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention (CDC) surveillance.[2]

Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) 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 neonatal period.[1, 3-7]

- Placental and breast milk passage

  In studies of women receiving atazanavir/ritonavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13% to 21% of maternal serum levels at delivery.[3, 5, 6] Atazanavir is excreted in the milk of lactating rats. In a study of three women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.[8]

- Human studies in pregnancy

  Several studies have investigated the pharmacokinetics (PKs) of atazanavir with ritonavir in pregnancy. In some of these studies, virological results were also analyzed. Overall, most pregnant patients were able to achieve HIV RNA less than 50 copies/mL at time of delivery.[9] In some studies, almost all pregnant patients achieved HIV RNA <50 copies/mL at time of delivery.[4, 6, 7] In a retrospective study reporting trough atazanavir concentrations in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg/day at a median of 30 weeks' gestation (14 in the third trimester), all but 2 women had a trough atazanavir concentration >100 ng/mL.[1] Three studies have evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy. In all of these studies, atazanavir AUC was lower during pregnancy than in historic data from HIV-infected non-pregnant patients.[3-5] In 1 of the 3 studies, there was no difference between atazanavir AUC during pregnancy and postpartum, but AUC at both times was lower than in non-pregnant HIV-infected historic controls.[3] In the other 2 studies, atazanavir AUC was 25% lower during pregnancy than in the same patients postpartum.[4, 5, 9] However, in both these studies (BMS AI424182 and IMPAACT P1026 atazanavir cohort), the postpartum AUC was elevated compared with non-pregnant HIV-infected historic control patients. For example, in study AI424182, 34 women were treated with 300 mg atazanavir plus 100 mg ritonavir at 4 to 12 weeks postpartum and were observed to have a 34% increase in geometric AUC compared with the historic control of HIV-infected, non-pregnant patients (62 µg*hr/mL vs. 46.1 µg*hr/mL respectively).[6] Because of the postpartum elevation in AUC in this study, the atazanavir drug label recommends that postpartum patients should be closely monitored for adverse events during the first 2 months after delivery.

  Although use of atazanavir with ritonavir combined with tenofovir and emtricitabine as a complete once-a-day dosing combination antiretroviral (ARV) regimen is becoming increasingly common in pregnancy, tenofovir reduces atazanavir exposure by 25% in non-pregnant adults.[10] This drug-drug interaction also is

present during pregnancy, with a 25% reduction in atazanavir AUC in pregnant women also receiving tenofovir compared with the same women postpartum and a 50% reduction compared with postpartum levels in women who did not receive tenofovir.[5]

Use of an increased dose of atazanavir of 400 mg with 100 mg ritonavir during pregnancy has been investigated in two studies.[4, 5] In both studies pregnant women receiving the increased dose without tenofovir had an atazanavir AUC equivalent to that seen in historic non-pregnant HIV-infected controls receiving standard-dose atazanavir without tenofovir. Pregnant women receiving the increased atazanavir dose with tenofovir had an AUC equivalent to that seen in non-pregnant HIV-infected patients receiving standard-dose atazanavir and tenofovir.[9]

In the prescribing information for atazanavir,[6] the dose recommended for most pregnant women is 300 mg with 100 mg of ritonavir. For additional details about dosing with interacting concomitant medications, please see Table 5 (Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy).

Neonatal elevations in bilirubin have been reported in some—but not all—studies of infants born to mothers receiving atazanavir during pregnancy.[3-5] Phototherapy was needed to control hyperbilirubinemia in 5 of 29 infants in 1 study.[7] In study AI424182, 6 of 39 infants received phototherapy.[4] Decisions to use phototherapy to treat infants with hyperbilirubinemia frequently are subjective and guidelines for phototherapy of infants vary between countries, making it difficult, therefore, to compare the severity of hyperbilirubinemia between patients within a study and in different studies. Elevated neonatal bilirubin is more likely in infants with uridine diphosphate glucuronosyltransferase 1 genotypes associated with decreased UGT function.[4]

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in 3 of 38 atazanavir-exposed infants with glucose samples collected in the first day of life. All three hypoglycemic infants' glucose samples were adequately collected and processed in a timely fashion (Bristol-Myers Squibb Reyataz product label). This finding of infant hypoglycemia is similar to a prior report in which 2 (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.[11]

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***Darunavir (Prezista, DRV)*** is classified as FDA Pregnancy Category C.

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

- 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 both male and female 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/day).

- 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 exposure via breast milk during lactation. In juvenile rats, single doses of darunavir (20 mg/kg–160 mg/kg at ages 5–11 days) or multiple doses of darunavir (40 mg/kg–1000 mg/kg at age 12 days) caused mortality. The deaths 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 cytochrome P450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring was not affected by maternal treatment. Fewer than 200 first-trimester pregnancy exposures have been reported to the Antiretroviral Pregnancy Registry; therefore, no conclusions can be made about risk of birth defects.

- Placental and breast milk passage
  No animal studies of placental passage of darunavir have been reported. Although variable transplacental

transfer of darunavir has been observed in some case reports, in a study of 14 mother/infant pairs the median (range) ratio of darunavir concentration in cord blood to that in maternal delivery plasma was 24% (6%–58%).[1, 2, 3, 4, 5] Passage of darunavir into breast milk has been noted in rats. It is unknown if breast milk passage of darunavir occurs in humans.

- Human studies in pregnancy
  Currently, limited data exist about darunavir in pregnancy.[1-11] Three intensive PK studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy demonstrate 17% to 35% reductions in darunavir plasma concentration during the third trimester compared with postpartum.[1, 4, 11] Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy. A study of use of an increased twice-daily darunavir dose during pregnancy is under way. Darunavir plasma protein binding decreases during pregnancy, which increases the unbound plasma darunavir fraction and may partially mitigate the decrease in total darunavir concentration.[11]

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***Fosamprenavir (Lexiva, FPV)*** is classified as FDA Pregnancy Category C.
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- 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 incidence of hepatocellular adenomas and 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 1400 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 1400 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. At those doses, no effect was seen on the development or maturation of sperm in rats.

- Teratogenicity/developmental toxicity
  Fosamprenavir was studied in rabbits at 0.8 times and in rats at twice 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 fetal loss and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at twice 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 with controls.

  The number of first-trimester exposures to fosamprenavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.[1]

- Placental and breast milk passage
  In a small study of women receiving fosamprenavir during pregnancy, the median (range) amprenavir concentration in cord blood was 0.27 (0.09–0.60) mcg/mL and the median (range) ratio of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery was 0.24 (0.06–0.93).[2]
  Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  Very limited data exist on fosamprenavir in pregnant women. Fosamprenavir PK data have been reported

in 16 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700 mg and ritonavir 100 mg, amprenavir AUC and 12-hour trough concentrations were somewhat lower during pregnancy and higher postpartum compared with historical data. Amprenavir exposure during pregnancy appeared to be adequate for patients without PI resistance mutations.[2]

A pediatric liquid formulation of fosamprenavir has been approved for children older than age 2 years, but there is no dosing information for neonates.

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***Indinavir (Crixivan, IDV)*** is classified as FDA Pregnancy Category C.

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- Animal carcinogenicity studies
  Indinavir is neither mutagenic nor 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 comparable to or slightly greater than therapeutic human exposure. 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 pregnant Rhesus monkeys during the third trimester (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 exacerbated 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. In Rhesus monkeys, fetal plasma drug levels were approximately 1% to 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. Among cases of first-trimester

indinavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.1% (6 of 286 births; 95% CI, 0.8%–4.5%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.[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 studies of pregnant women receiving unboosted indinavir and their infants, transplacental passage of indinavir was minimal.[2, 3] In a study of Thai pregnant women receiving indinavir boosted with ritonavir, median cord blood indinavir concentration was 0.12 mcg/mL, median maternal plasma delivery concentration was 0.96 mcg/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 12%.[4] Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26–1.45); 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. Two studies of the PKs of unboosted indinavir (800 mg 3 times a day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum.[2, 5] Use of unboosted indinavir is not recommended in HIV-infected pregnant patients because of the substantially lower antepartum exposures observed in these studies and the limited experience in this patient population.

  Several reports investigate the use of indinavir with ritonavir boosting during pregnancy. In an intensive PK study of 26 Thai pregnant women receiving 400 mg indinavir/100 mg ritonavir twice a day, indinavir plasma concentrations were significantly lower during pregnancy than postpartum. The median trough indinavir concentration was 0.13 mcg/mL; 24% of subjects had trough concentrations below 0.10 mcg/mL, the target trough concentration used in therapeutic drug monitoring (TDM) programs; and 81% had RNA viral loads <50 copies/mL at delivery.[4] In a study of French pregnant women receiving 400 mg indinavir/100 mg ritonavir twice a day, the median indinavir trough concentration was 0.16 mcg/mL, 18% of subjects had trough concentrations below 0.12 mcg/mL, and 93% had HIV RNA level < 200 copies/mL at delivery.[6] In a small study of 2 women who received indinavir 800 mg and ritonavir 200 mg twice daily, third-trimester indinavir AUC exceeded that for historical non-pregnant controls.[7] Based on these data, indinavir can be used in pregnancy with ritonavir boosting. Given the limited data on appropriate dosing, HIV RNA levels and trough indinavir concentrations should be monitored during indinavir use in pregnancy.

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## ***Lopinavir + Ritonavir (Kaletra, LPV/r)*** is classified as FDA Pregnancy Category C.

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- Animal carcinogenicity studies
  Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increased incidence of benign hepatocellular adenomas and increased combined incidence of hepatocellular adenomas plus carcinoma in male and female mice and male 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 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
  No evidence exists of teratogenicity with administration of lopinavir/ritonavir to pregnant rats or rabbits. In rats treated with a 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 exposure to 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a 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 for detection of at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with lopinavir/ritonavir. Among cases of first-trimester lopinavir/ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.4% (21 of 883; 95% CI, 1.5%–3.6%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance.[1]

- Placental and breast milk passage
  Lopinavir crosses the human placenta; in the P1026s PK study, 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 original capsule formulation of lopinavir/ritonavir has been replaced by a new tablet formulation that is heat stable, has improved bioavailability characteristics, and does not have to be administered with food.[2, 3] PK studies of standard adult lopinavir/ritonavir doses (400 mg/100 mg twice a day ) using either the capsule or tablet formulations in pregnant women have demonstrated a reduction in lopinavir plasma concentrations during pregnancy of around 30% compared with that in non-pregnant adults.[4-6] Increasing lopinavir/ritonavir doses during pregnancy to either 533 mg/133 mg (capsules) or 600 mg/150 mg (tablets) results in lopinavir plasma concentrations equivalent to those seen in non-pregnant adults receiving standard doses.[7, 8] Reports of clinical experience suggest that most but not all pregnant women receiving standard lopinavir/ritonavir tablet dosing during pregnancy will have trough lopinavir concentrations that exceed 1.0 mcg/mL, the usual trough concentration target used in therapeutic drug monitoring programs for ARV-naive subjects, but not the higher trough concentrations recommended for PI-experienced subjects.[2, 5] Lopinavir plasma protein binding is reduced during pregnancy, but the resulting increase in free (unbound) drug is insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.[9, 10]

These PK studies suggest that lopinavir/ritonavir doses should be increased to 600 mg/150 mg twice a day in all HIV-infected pregnant women during the second and third trimesters. If standard doses of lopinavir/ritonavir are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy for increasing lopinavir/ritonavir exposure during pregnancy is to add a pediatric lopinavir/ritonavir tablet (100/25 mg) to the standard dose of two adult 200/50 mg tablets.[10] Once-daily dosing of lopinavir/ritonavir is not recommended in pregnancy because no data exist to address whether drug levels are adequate with such administration.

Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Reduced hepatic metabolic and kidney excretory function in newborns can lead to accumulation of lopinavir as well as alcohol and propylene glycol, resulting in adverse events such as serious cardiac, renal, metabolic, or respiratory problems. Preterm babies may be at increased risk because their metabolism and elimination of lopinavir, propylene glycol, and alcohol are further reduced. Postmarketing surveillance has identified 10 neonates (babies <4 weeks of age), 9 of whom were born prematurely, who received lopinavir/ritonavir and experienced life-threatening events.[11] In a separate report comparing 50 HIV-exposed newborns treated with lopinavir/ritonavir after birth to 108 HIV-exposed neonates treated with zidovudine alone, elevated concentrations of 17-hydoxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21α-hydroxylase activity, were seen only in the lopinavir-exposed infants. All term infants were asymptomatic but 3 of 8 preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.[12] Lopinavir/ritonavir oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth, plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

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***Nelfinavir (Viracept, NFV)*** is classified as FDA Pregnancy Category B.

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

- Animal carcinogenicity studies
  Nelfinvair was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, incidence of thyroid follicular cell adenomas and carcinomas was increased over baseline in male rats receiving nelfinavir dosages of 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses).

- 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. Maternal exposure to nelfinavir also did not affect subsequent reproductive performance of the offspring.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to human exposure and in rabbits with exposures significantly less than human exposure.

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. Among cases of first-trimester nelfinavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 3.9% (47 of 1,204 births; 95% CI, 2.9%–5.2%) compared with a 2.7% total prevalence in the U.S. population, based on CDC surveillance.[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] In addition, in a study of cord blood samples from 38 women treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 µg/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 PK study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants.[2] In the first nine pregnant HIV-infected women enrolled in the study, nelfinavir administered at a dose of 750 mg three times daily produced drug exposures that were variable and generally lower than those reported in non-pregnant adults with both twice- and three-times-daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1250 mg twice daily), which resulted in adequate levels of the drug in pregnancy. However, in two other small studies of women given 1250 mg nelfinavir twice daily in the second and third trimesters, drug concentrations in the second and third trimesters were somewhat lower than in non-pregnant women.[4, 5]

  In a PK study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1250 mg twice daily) in 25 women at 30 to 36 weeks' gestation (and 12 at 6–12 weeks postpartum), peak levels and AUC were lower in the third trimester than postpartum.[6] Only 16% (4 of 25) of women during the third trimester and 8% (1 of 12) women postpartum had trough values greater than the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

  Some nelfinavir manufactured before 2008 may have contained low levels of ethyl methane sulfonate (EMS), a process-related impurity. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data exist in humans and no increase in birth defects has been observed in the Antiretroviral Pregnancy Registry. All nelfinavir manufactured and released since March 31, 2008, meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients.

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## ***Ritonavir (Norvir, RTV)*** is classified as FDA Pregnancy Category B.

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

- 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, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at levels of 50, 100, or 200 mg/kg/day; 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 recommended therapeutic human exposure.

- 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 because of hepatic toxicity in the rodents.

- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles, was observed in rats; 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. No such increase in birth defects has been observed with ritonavir. Among cases of first-trimester ritonavir exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (39 of 1,741 births; 95% CI, 1.6%–3.0%) compared with a total prevalence of 2.7% in the U.S. population, based on CDC surveillance.[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 of 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 less

than the assay limit of detection in 83% and was only 0.38 µg/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 PK study (PACTG 354) of ritonavir (500 or 600 mg twice daily) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy than postpartum.[3] Ritonavir concentrations are also reduced during pregnancy versus postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other PIs.[5, 6]

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***Saquinavir (Invirase, SQV)*** is classified as FDA Pregnancy Category B.

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

- 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 of 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.

Too few first-trimester saquinavir exposures have been monitored by the Antiretroviral Pregnancy Registry to be able to accurately calculate the prevalence of birth defects in exposed cases.[1]

- 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.[2] In addition, in a study of cord blood samples from eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was less than the assay limit of detection in samples from all women.[3] 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 PKs of saquinavir-hard gel capsules (HGC) combined with low-dose ritonavir (saquinavir-HGC 1000 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.[4, 5] In a small study of 2 women who received saquinavir-HGC 1200 mg/ritonavir 100 mg given once daily, trough levels were 285 and 684 ng/mL and the $AUC_{0–24}$ were 28,010 and 16,790 ng hour/mL, greater than the target AUC of 10,000 ng hour/mL.[6] Thus, the limited available data suggest that saquinavir-HGC 1000 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 1200 mg/100 mg ritonavir combined with various nucleoside reverse transcriptase inhibitors during 46 pregnancies demonstrated saquinavir levels greater than the target minimum plasma concentration in 46 (93.4%) of pregnancy episodes and undetectable viral load at delivery in 88% of episodes.[7] Target levels were achieved in the other 3 women with a dose of 1600 mg/100 mg. The drug was well tolerated.

  The PKs of the new 500-mg tablet formulation of saquinavir boosted with ritonavir in a dose of saquinavir 1000 mg/ritonavir 100 mg given twice daily were studied in 37 HIV-infected pregnant women at 20 and 33 weeks' gestation and 6 weeks postpartum; PK parameters were comparable during pregnancy and postpartum.[8] However, in a smaller study of saquinavir tablets boosted with ritonavir given to 14 HIV-infected pregnant women, the saquinavir exposure during the third trimester was reduced by about 50%, yet no woman experienced loss of virologic control and all but 1 maintained adequate trough levels of saquinavir.[9] Thus, it does not appear that any adjustment of saquinavir boosted with ritonavir is necessary during pregnancy.

  One study of a saquinavir/ritonavir-based combination ARV drug regimen 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, Grade 3 in 1 woman).[10]

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***Tipranavir (Aptivus, TPV)*** is classified as FDA Pregnancy Category C.

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

- 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. Incidence of benign hepatocellular adenomas and combined adenomas/carcinomas was increased in females of all groups except females given the low dose of tipranavir. Such tumors also were increased in male mice at the high dose of tipranavir and in the tipranavir/ritonavir combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in 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 maximum plasma concentration) 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 were observed in male rats. 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/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. Fetal toxicity (decreased ossification and body weights) was observed in rats exposed to 400 mg/kg/day or more of tipranavir (~0.8-fold human exposure). Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold human exposures. In rats, no adverse effects on development were seen at levels of 40 mg/kg/day (~0.2-fold human exposure), but at 400 mg/kg/day (~0.8-fold human exposure), growth inhibition in pups and maternal toxicity were seen.

- 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 completed in pregnant women or neonates. A case report with PK measurements of tipranavir used in a single pregnancy showed relatively high levels of tipranavir third trimester and relatively high placental transfer (0.41), as measured by cord blood.[1] It is unclear whether this finding will be applicable to other pregnancies.

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