



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

Carcinogenic = producing or tending to produce cancer

- Some agents, such as certain chemicals or forms of radiation, are both mutagenic and clastogenic.
- Genetic mutations and/or chromosomal damage can contribute to cancer formation.

Clastogenic = causing disruption of or breakages in chromosomes

Genotoxic = damaging to genetic material such as DNA and chromosomes

Mutagenic = inducing or capable of inducing genetic mutation

Teratogenic = interfering with fetal development and resulting in birth defects

For information regarding the PI class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see [Combination Antiretroviral Drug Regimens and Pregnancy Outcome](#).

Amprenavir (Agenerase, APV)

(Last updated March 28, 2014; last reviewed March 28, 2014)

Amprenavir is no longer available in the United States.

Atazanavir (Reyataz, ATV)

(Last updated August 6, 2015; last reviewed August 6, 2015)

Atazanavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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 atazanavir boosted with 100 mg ritonavir once daily). There was no increase 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.¹

Reproduction/Fertility

No effect of atazanavir on reproduction or fertility in male and female rodents was seen at area under the curve (AUC) levels that were 0.9-fold in males and 2.3-fold in females compared with the exposures achieved in humans at the recommended therapeutic dose.¹

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 atazanavir boosted with 100 mg ritonavir once daily). 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.¹ A more recent study demonstrated an association of maternal PI use (including atazanavir) with lower progesterone levels which correlated with lower birthweight in mice, but this potential mechanism requires further study.²

Placental and Breast Milk Passage

Atazanavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Several studies have investigated the pharmacokinetics (PKs) and virologic outcomes of ritonavir-boosted atazanavir in pregnancy.³ Overall, most pregnant patients achieved undetectable HIV RNA at the time of delivery.^{1,4-7} In a retrospective study reporting trough atazanavir concentrations in 19 pregnant women receiving atazanavir 300 mg and ritonavir 100 mg once daily at a median of 30 weeks' gestation (14 in the third trimester), all but two women had a trough atazanavir concentration >100 ng/mL.⁸ In studies that have evaluated full PK profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy, atazanavir AUC was lower during pregnancy than in historic data from HIV-infected non-pregnant patients.^{4,6,7,9,10} In one of the 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.⁶ In the other studies, atazanavir AUC was lower during pregnancy than in the same patients postpartum and in non-pregnant control populations.^{4,5,7,9,10}

Although use of atazanavir/ritonavir combined with tenofovir **disoproxil fumarate (tenofovir)** and emtricitabine as a complete once-a-day dosing combination antiretroviral therapy (cART) regimen is becoming increasingly common in pregnancy, tenofovir reduces atazanavir exposure by 25% in non-pregnant adults.⁹ This drug-drug interaction also is present during pregnancy, with a **30% lower third-trimester atazanavir AUC in pregnant women receiving concomitant tenofovir compared with women who were not receiving concomitant tenofovir.** **The increase in atazanavir AUC postpartum relative to that in the third trimester was similar for women taking concomitant tenofovir and for those not taking concomitant tenofovir.**⁷

Use of an increased dose of atazanavir of 400 mg with 100 mg ritonavir once daily 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 with tenofovir.^{4,5} Although some experts recommend increased atazanavir dosing in all women during the second and third trimesters, the package insert recommends increased atazanavir dosing only for ARV-experienced pregnant women in the second and third trimesters also receiving either tenofovir or an H2-receptor antagonist. For additional details about dosing with interacting concomitant medications, please see [Table 7. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.](#)

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.^{1,6,7}

In a study of three women, the median ratio of breast milk atazanavir concentration to that in plasma was 13%.¹¹

Teratogenicity/Developmental Toxicity

In a multicenter U.S. cohort of HIV-exposed, uninfected children, first trimester atazanavir exposure was associated with increased odds of congenital anomalies of skin (aOR = 5.24, $P = 0.020$) and musculoskeletal system (aOR = 2.55, $P = 0.007$).¹² On the other hand, there was no association of first-trimester atazanavir exposure and birth defects in a French cohort, though this study had <50% power to detect an adjusted odds ratio of 1.5.¹³ The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to atazanavir in humans to be able to detect at least a 2-fold increase in risk of overall birth defects and no such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with

first-trimester atazanavir exposure was 2.2% (20 of 922 births; 95% confidence interval [CI], 1.3% to 3.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.¹⁴

Maternal PI use (including atazanavir) was associated with lower progesterone levels, but the clinical significance of this finding requires further study.²

Other Safety Data

Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT) enzyme occurs frequently during treatment with atazanavir, including during pregnancy.¹⁵ The effects on the fetus of elevated maternal indirect bilirubin throughout pregnancy are unknown. Dangerous or pathologic postnatal elevations in bilirubin have not been reported in infants born to mothers who received atazanavir during pregnancy.^{1,4,6-8,16-18} Although some studies have suggested that neonatal bilirubin elevations requiring phototherapy occur more frequently after prenatal atazanavir exposure, decisions to use phototherapy to treat infants with hyperbilirubinemia frequently are subjective and guidelines for phototherapy of infants vary between countries, making it difficult to compare the severity of hyperbilirubinemia between patients within a study and in different studies.^{16,17} Elevated neonatal bilirubin in atazanavir-exposed neonates is not associated with UGT-1 genotypes associated with decreased UGT function.¹⁸

In an evaluation of neurodevelopment in 374 HIV-exposed uninfected infants aged 9 to 15 months, the adjusted mean on the language domain of the Bayley-III test was significantly lower for infants with perinatal exposure to atazanavir compared to those with exposure to other drugs.¹⁹ In a study of language assessments among 792 one- and 2-year-old HIV-exposed uninfected children, atazanavir-exposed children had an increased risk of late language emergence at age 12 months (adjusted odds ratio 1.83, 95% CI, 1.10–3.04) compared with atazanavir-unexposed children but the association was not significant at 24 months.²⁰

Hypoglycemia (glucose <40 mg/dL) that could not be attributed to maternal glucose intolerance, difficult delivery, or sepsis has been reported in three 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.¹ This finding of infant hypoglycemia is similar to a prior report in which two (both nelfinavir) of 14 infants exposed to PIs (nelfinavir, saquinavir, and indinavir) developed hypoglycemia in the first day of life.²¹

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Darunavir (Prezista, DRV)

(Last reviewed August 6, 2015; last updated August 6, 2015)

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

Animal Studies

Carcinogenicity

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 area under the curve) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats) 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 prenatal 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 age 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.

Placental and Breast Milk Passage

No animal studies of placental passage of darunavir have been reported. Passage of darunavir into breast milk has been noted in rats.

Human Studies in Pregnancy

Pharmacokinetics

Three intensive pharmacokinetic (PK) studies of darunavir/ritonavir administered as 600 mg/100 mg twice a day or 800 mg/100 mg once a day during pregnancy have been completed.¹⁻³ These studies demonstrate **17% to 33%** reductions in darunavir plasma concentrations during the third trimester compared with postpartum.¹⁻³ **Two of these studies measured darunavir protein binding during pregnancy with conflicting results. One study found no change in darunavir protein binding during the third trimester while the other found a decrease.**¹⁻⁴ Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, **especially for antiretroviral-experienced patients.** A study of use of an increased twice-daily darunavir dose during pregnancy is underway. **The PK and safety of darunavir/cobicistat during pregnancy have not been studied.**

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate was 15%.⁵ In 4 studies reporting data from between eight and 14 subjects each, the median ratio of darunavir concentration in cord blood to that in maternal delivery plasma ranged from 13% to 24%.¹⁻⁴ No data are available describing breast milk passage of darunavir in humans.

Teratogenicity Data

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.3% (6 of 258 births; 95% CI, 0.9% to 5.0%) compared with 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁶

Other Safety Issues

No safety issues have been observed in case reports and small PK studies of darunavir in pregnancy.^{1-4,7-11}

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Fosamprenavir (Lexiva, FPV)

(Last updated August 6, 2015; last reviewed August 6, 2015)

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

Animal Studies

Carcinogenicity

Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only, there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus, the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7 (mice) and 0.7- to 1.4 (rats) times those in humans given 1,400 mg twice daily of fosamprenavir alone and were 0.2- to 0.3 (mice) and 0.3- to 0.7 (rats) times those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3 (mice) and 0.3- to 0.6 (rats) times those in humans given 700 mg fosamprenavir plus 100 mg ritonavir twice daily.

Reproduction/Fertility

No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No effect 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 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 abortions 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 to controls.

Placental and Breast Milk Passage

Amprenavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Data on fosamprenavir in pregnant women are very limited. Fosamprenavir pharmacokinetic data have been reported in 26 women during pregnancy and postpartum. Following standard dosing with fosamprenavir 700 mg and ritonavir 100 mg, fosamprenavir area under the curve and 12-hour trough concentration were somewhat lower during pregnancy and higher postpartum, compared to historical data. Fosamprenavir exposure during pregnancy appeared to be adequate for patients without protease inhibitor resistance mutations.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) µg/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).¹ A second small study in pregnancy yielded a similar mean ratio (95% confidence interval) of amprenavir concentration in cord blood to that in maternal plasma at the time of delivery of 0.27 (0.24, 0.30).² Whether amprenavir is excreted in human breast milk is unknown.

Teratogenicity/Developmental Toxicity

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 the risk of birth defects.³

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Indinavir (Crixivan, IDV)

(Last updated August 6, 2015; last reviewed August 6, 2015)

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

Animal Studies

Carcinogenicity

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 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 caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester. 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.

Placental and Breast Milk Passage

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26 to 1.45).

Human Studies in Pregnancy

Pharmacokinetics

The optimal dosing regimen for use of indinavir in pregnant patients has not been established. Two studies of the pharmacokinetics (PKs) of unboosted indinavir (800 mg 3 times/day) during pregnancy demonstrated significantly lower indinavir plasma concentrations during pregnancy than postpartum.^{1,2} 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 have investigated use of indinavir/ritonavir (IDV/r) 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 µg/mL; 24% of subjects had trough concentrations below 0.10 µg/mL, the target trough concentration used in therapeutic drug monitoring programs; and 81% had RNA viral loads <50 copies/mL at delivery.³ In a study of pregnant French women receiving 400 mg indinavir/100 mg ritonavir twice a day, the median indinavir trough concentration was 0.16 µg/mL, 18% of subjects had trough concentrations below 0.12 µg/mL, and 93% had HIV RNA level <200 copies/mL at delivery.⁴ In a small

study of 2 patients who received indinavir 800 mg and ritonavir 200 mg twice daily, third-trimester indinavir area under the curve exceeded that for historical non-pregnant controls.⁵ The available data are insufficient to allow for definitive dosing recommendations for use of IDV/r during pregnancy.

Placental and Breast Milk Passage

In studies of pregnant women receiving unboosted indinavir and their infants, transplacental passage of indinavir was minimal.^{1,6} In a study of Thai pregnant women receiving IDV/r, median cord blood indinavir concentration was 0.12 µg/mL, median maternal plasma delivery concentration was 0.96 µg/mL, and the median ratio between indinavir concentrations in cord blood and maternal plasma at delivery was 0.12.³ **It is unknown whether indinavir is excreted in human milk.**

Teratogenicity/Developmental Toxicity

Although the French Perinatal Cohort reported an association of head and neck birth defects with first trimester exposure to indinavir (3 defects in 350 first-trimester exposures, 0.9%), the Antiretroviral Pregnancy Registry has not observed an increase in birth defects with indinavir.^{7,8} Among cases of first-trimester indinavir exposure reported to the Antiretroviral Pregnancy Registry, defects have been seen in 2.4% (7/289; 95% CI, 1.0% to 4.9%) compared to total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention surveillance of 2.7%.⁸

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Lopinavir/Ritonavir (Kaletra, LPV/r)

(Last updated August 6, 2015; last reviewed August 6, 2015)

Lopinavir/ritonavir (LPV/r) is classified as Food and Drug Administration Pregnancy Category C.

Animal Studies

Carcinogenicity

Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. The LPV/r 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 area under the curve [AUC]_{0–24hr} measurement). Administration of LPV/r did not cause a statistically significant increase in incidence of any other benign or malignant neoplasm in mice or rats.¹

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.¹

Teratogenicity/Developmental Toxicity

No evidence exists of teratogenicity with administration of LPV/r 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 (e.g., 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 perinatal 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.¹ In a study of pregnant rats receiving chronic administration of zidovudine, lopinavir, and ritonavir, maternal body weight gain was significantly reduced, but no adverse fetal parameters were observed.² In pregnant mice, ritonavir, lopinavir and atazanavir were associated with significantly lower progesterone levels, and the lower progesterone levels directly correlated with lower fetal weight.³

Placental and Breast Milk Passage

No information is available on placental transfer of lopinavir in animals. Studies in rats show secretion of lopinavir in breast milk.¹

Human Studies in Pregnancy

Pharmacokinetics

The original capsule formulation of LPV/r has been replaced by a tablet formulation that is heat-stable, has improved bioavailability characteristics, and does not have to be administered with food.^{4,5} Pharmacokinetic (PK) studies of standard adult LPV/r 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.^{6–8} Further reductions in lopinavir exposure by 33% were demonstrated in food-insecure, malnourished pregnant women in Uganda compared to well-nourished, historical pregnant controls. The authors attributed this reduction to decreased bioavailability.⁹ Increasing dose of LPV/r during pregnancy to 600 mg/150 mg (tablets) results in lopinavir plasma concentrations equivalent to those seen in non-pregnant adults receiving standard doses.^{10,11} Reports

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

of clinical experience suggest that most, but not all, pregnant women receiving standard LPV/r 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 antiretroviral-naïve subjects, but not the higher trough concentrations recommended for protease inhibitor (PI)-experienced subjects.^{4,7} A population PK study of LPV/r in 154 pregnant women demonstrated that body weight influences lopinavir clearance and volume, with larger women (>100 kg) or women who missed a dose at higher risk for subtherapeutic trough concentrations when taking the standard dose during pregnancy.¹² In one study of 29 women, lopinavir plasma protein binding was reduced during pregnancy, but the resulting increase in free (unbound) drug was insufficient to make up for the reduction in total plasma lopinavir concentration associated with pregnancy.¹³ In a study of 12 women, total lopinavir exposure was significantly decreased throughout pregnancy, but unbound AUC and C₁₂ did not differ throughout pregnancy, even with an increased dose of 500/125 mg.¹⁴ Bonafe, et al. randomized 32 pregnant women to standard dose and 31 pregnant women to the 600/150 mg dose of LPV/r at gestational ages between 14 and 33 weeks. No differences in adverse events were seen between groups. In women with baseline viral loads >50 copies/mL, 45% in the standard dose group had plasma viral loads >50 copies/mL during the last 4 weeks of pregnancy, compared to 10.5% in the increased dose group (*P* = 0.01). In women with baseline viral loads <50 copies/mL, no difference was seen between groups in viral load measurements in the last 4 weeks of pregnancy.¹⁵

These studies have led some experts to support use of an increased dose of LPV/r in HIV-infected pregnant women during the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. If standard doses of LPV/r are used during pregnancy, virologic response and lopinavir drug concentrations, if available, should be monitored. An alternative strategy to increasing LPV/r dosing during pregnancy by using 3 adult 200/50 mg tablets to provide a dose of 600/150 mg is to add a pediatric LPV/r tablet (100/25 mg) to the standard dose of 2 adult 200/50 mg tablets to provide a dose of 500/125 mg.¹⁴ Once-daily dosing of LPV/r **is not recommended** in pregnancy because no data exist to address whether drug levels are adequate with such administration.

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. In contrast, in a study of plasma and hair drug concentration in 51 mother-infant pairs in Uganda receiving LPV/r during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested significant in utero transfer: 41% of infants had detectable plasma lopinavir concentrations at birth and mean infant-to-maternal-hair concentrations at 12 weeks postpartum were 0.87 for lopinavir.¹⁶ However, transfer during breastfeeding was not observed, and no infant had detectable plasma lopinavir levels at 12 weeks. Lopinavir concentrations in human breast milk are very low to undetectable and lopinavir concentrations in breastfeeding infants whose mothers received lopinavir are not clinically significant.¹⁶⁻²⁰

Teratogenicity/Developmental Toxicity

The French Perinatal Cohort found no association between birth defects and lopinavir or ritonavir with 85% power to detect a 1.5-fold increase.²¹ The Pediatric HIV/AIDS Cohort Study found no association between lopinavir and congenital anomalies.²² In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to LPV/r 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 LPV/r. Among cases of first-trimester exposure to LPV/r reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (26 of 1174; 95% CI, 1.4% to 3.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²³

Safety

LPV/r 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. Post-marketing surveillance has identified 10 neonates (i.e., babies aged <4 weeks), nine of whom were born prematurely, who received LPV/r and experienced life-threatening events.²⁴ In a separate report comparing 50 HIV-exposed newborns treated with LPV/r after birth to 108 HIV-exposed neonates treated with zidovudine alone, elevated concentrations of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate, consistent with impairment of 21 α -hydroxylase activity, were seen only in the lopinavir-exposed infants. All term infants were asymptomatic but three of eight preterm infants had life-threatening symptoms, including hyponatremia, hyperkalemia, and cardiogenic shock, consistent with adrenal insufficiency.²⁵ LPV/r 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)

(Last updated August 6, 2015; last reviewed August 6, 2015)

Nelfinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

Nelfinavir 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 mid-pregnancy 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.

Human Studies in Pregnancy

Pharmacokinetics

A Phase I/II safety and pharmacokinetic (PK) study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants.¹ In the first 9 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.^{2,3}

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 area under the curve were lower in the third trimester than postpartum.⁴ Only 16% (4 of 25) of women during the third trimester and 8% (1/12) of 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.

Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 353), transplacental passage of nelfinavir was minimal.¹ 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.⁵ Among 20 mother-infant pairs in the Netherlands, the cord blood-to-maternal-plasma ratio for nelfinavir was 0.14 compared to 0.67 for nevirapine and 0.24 for lopinavir.⁶

Nelfinavir also has low breast milk passage. In a PK study conducted in Kisumu, Kenya, concentrations of nelfinavir and its active metabolite, M8, were measured in maternal plasma and breast milk from 26 mothers receiving nelfinavir as part of combination antiretroviral therapy and from their 27 infants at birth, 2, 6, 14, and 24 weeks.⁷ Peak nelfinavir concentrations were recorded in maternal plasma and breast milk at Week 2. Median breast milk-to-plasma ratio was 0.12 for nelfinavir and 0.03 for its active metabolite (i.e., M8). Nelfinavir and M8 concentrations were below the limit of detection in 20/28 (71%) of infant plasma dried blood spots tested from nine infants over time points from delivery through Week 24. Overall transfer to breast milk was low and resulted in non-significant exposure to nelfinavir among breastfed infants through age 24 weeks.

Teratogenicity/Developmental Toxicity

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increased risk of birth defects in the more common classes of birth defects—the cardiovascular and genitourinary systems. 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 1,214 births; 95% CI, 2.8% to 5.1%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

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Saquinavir (Invirase, SQV)

(Last updated August 6, 2015; last reviewed August 6, 2015)

Saquinavir is classified as Food and Drug Administration Pregnancy Category B.

Animal Studies

Carcinogenicity

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 (area under the curve [AUC] values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Placental and Breast Milk Passage

Placental transfer of saquinavir in the rat and rabbit was minimal. Saquinavir is excreted in the milk of lactating rats.

Human Studies in Pregnancy

Pharmacokinetics

Studies of saquinavir pharmacokinetics (PK) in pregnancy with the original hard-gel capsule formulation demonstrated reduced saquinavir exposures compared to postpartum and dosing recommendations for 800 to 1200 mg saquinavir with 100 mg ritonavir.¹⁻⁵ The PK of saquinavir with the current 500-mg tablets boosted with ritonavir at a dose of 1000 mg saquinavir/100 mg ritonavir given twice daily has been studied in pregnant women in two studies.^{6,7} One study performed intensive sampling on HIV-infected pregnant women at 20 weeks' gestation (n = 16), 33 weeks' gestation (n = 31), and 6 weeks postpartum (n = 9). PK parameters were comparable during pregnancy and postpartum.⁶ The second study performed intensive sampling in 14 pregnant women at 24 and 34 weeks' gestation and 6 weeks postpartum. Saquinavir AUC was similar during the second trimester and postpartum. Although there was a 50% reduction in saquinavir AUC in the third trimester compared to postpartum, no subject experienced loss of virologic control and all but one maintained adequate third-trimester trough levels of saquinavir.⁸ In an observational study of saquinavir concentrations collected as part of clinical care between 11 and 13 hours after dosing with the tablet formulation (1000 mg saquinavir/100 mg ritonavir) in HIV-infected pregnant women during the third trimester (n = 20) and at delivery (n = 5), saquinavir plasma concentrations averaged around 1.15 mg/L and exceeded the usual trough drug concentration target for saquinavir of 0.1 mg/L in all but one subject.⁷

One study of 42 pregnant women receiving a combination antiretroviral drug regimen that included ritonavir-boosted saquinavir 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).⁹ In a study of 62 pregnant women on a regimen that included saquinavir/ritonavir, one severe

adverse event occurred (maternal Grade 3 hepatotoxicity).⁷

Placental and Breast Milk Passage

In a Phase I study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.¹⁰ In addition, in a study of 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.¹¹ It is not known if saquinavir is excreted in human milk.

Teratogenicity/Developmental Toxicity

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.¹²

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Tipranavir (Aptivus, TPV)

(Last reviewed August 6, 2015; last updated August 6, 2015)

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

Animal Studies

Carcinogenicity

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 (TPV/r) 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 TPV/r combination group. Incidence of hepatocellular carcinoma was increased in female mice given the high dose of tipranavir and in both sexes receiving TPV/r. 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 area under the curve [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 TPV/r 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 area under the curve 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 TPV/r **BID**).

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 Passage

No animal studies of placental or breast milk passage of tipranavir have been reported.

Human Studies in Pregnancy

Pharmacokinetics

No studies of tipranavir have been completed in pregnant women or neonates.

Placental and Breast Milk Passage

It is unknown if passage of tipranavir through the placenta or breast milk occurs in humans. A single case report described relatively high levels of tipranavir in the third trimester and relatively high placental transfer (0.41), as measured by cord blood.¹

Teratogenicity/Developmental Toxicity

The number of first-trimester exposures to tipranavir that have been monitored to date in the Antiretroviral Pregnancy Registry is insufficient to allow conclusions to be drawn regarding risk of birth defects.²

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