The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women *[60-62]*. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2 fold more common in women than men *[63]*. The degree of risk for hepatic toxicity varies with $CD4^+$ cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with $CD4^+$ counts greater than 250 cells/mm^3 were 9.8 times more likely than women with lower $CD4^+$ counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity *[63]*. Higher $CD4^+$ cell counts have also been associated with increased risk of severe nevirapine-associated skin rash *[61]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5-11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, ranging between 0.04-0.40% *[63, 64]*. Severe or life threatening rash occurs in approximately 2% of patients receiving nevirapine *[64]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs *[65, 66]*. Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase, ALT and aspartate aminotransferase, AST), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through 4 months, and every 1 to 3 months thereafter [**Adult Antiretroviral Guidelines**]; in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy, and then monthly *[67]*. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST), or have asymptomatic but severe transaminase elevations, should stop nevirapine and not receive nevirapine therapy in the future.

Nevirapine should be used with caution in pregnant antiretroviral-naïve women who are being started on combination antiretroviral therapy for the purpose of preventing perinatal HIV transmission, but who have $CD4^+$ counts that would not otherwise indicate that they require therapy for their own health (see **Adult Antiretroviral Guidelines**).

PROTEASE INHIBITORS

Issues Related to the Use of Protease Inhibitors

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with administration of protease inhibitor antiretroviral drugs in HIV-infected patients *[68-71]*. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia. Clinicians caring for HIV-infected pregnant women who are receiving protease inhibitor therapy should be aware of the risk of this complication, and closely monitor glucose levels. Symptoms of hyperglycemia should be discussed with pregnant women who are receiving protease inhibitors.

Combination Therapy and Pregnancy Outcome:

There are limited data concerning combination antiretroviral therapy in pregnancy. A retrospective Swiss report evaluated the pregnancy outcome in 37 HIV-infected pregnant women treated with combination therapy; all received two reverse transcriptase inhibitors and 16 received one or two protease inhibitors *[72]*. Almost 80% of women developed one or more typical adverse effects of the drugs such as anemia, nausea/vomiting, aminotransferase elevation, or hyperglycemia. A possible association of combination antiretroviral therapy with preterm births was noted, as 10 of 30 babies were born prematurely. The preterm birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV disease stage and other covariates that might be associated with a risk for prematurity were not assessed. Furthermore, some studies have shown elevated preterm birth rates in HIV-infected women who have not received any antiretroviral therapy *[73-75]*.

The European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study investigated the effects of combination retroviral therapy in a population of 3,920 mother - child pairs. Adjusting for $CD4^+$ T-lymphocyte count ($CD4^+$ count) and intravenous drug use, they found a 2.6-fold (95% confidence interval [CI] = 1.4 - 4.8) increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors compared with no treatment; women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester *[76]*. However, combination therapy was received by only 323 (8%) women studied. Exposure to monotherapy was not associated with prematurity.

In contrast, in a French open-label study of 445 HIV-1-infected women receiving ZDV who had lamivudine (3TC) added to their therapy at 32 weeks' gestation, the rate of preterm delivery was 6%, similar to the 9% rate in a historical control group of women receiving only ZDV *[77]*. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-infected pregnant women who delivered infants during 1990-1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, use of multiple antiretroviral drugs as compared with no treatment or treatment with one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth *[78]*.

Until more information is known, it is recommended that HIV-infected pregnant women who are receiving combination therapy for treatment of their HIV infection should continue their provider-recommended regimen. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Individual Agents: Protease Inhibitors

Phase I studies of four of the approved protease inhibitors (indinavir, ritonavir, nelfinavir and saquinavir soft gel capsule in combination with ZDV and 3TC) in pregnant HIV-infected women and their infants are ongoing in the United States. However, complete data are not yet available regarding drug dosage, safety, and tolerance of the protease inhibitors in pregnancy or in neonates. Amprenavir, atazanavir, and lopinavir/ritonavir (Kaletra™), two more recently approved protease inhibitors, have not yet been studied in pregnant women or neonates.

Amprenavir (Agenerase®) is classified as FDA pregnancy category C.

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

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

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

- Placental and breast milk passage
  Whether amprenavir crosses the placenta is unknown. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  There have been no studies of amprenavir in pregnant women or neonates. Amprenavir oral solution contains high levels of excipient propylene glycol in the oral solution vehicle; this is not true for the capsular formulation. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below the age of four years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are not able to adequately metabolize and eliminate propylene glycol, thereby

leading to its accumulation and potential adverse events. Thus, while the capsule formulation of amprenavir may be used in pregnancy, amprenavir oral solution is contraindicated in pregnant women and infants and in children under the age of four years.

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

- Animal carcinogenicity studies
  Long-term carcinogenicity studies of atazanavir have not been completed. Atazanavir tested positive in an *in vitro* clastogenicity assay using human lymphocytes, but negative in several mutagenicity assays (Ames reverse-mutation assay, micronucleus and DNA repair tests in rats).

- Reproduction/fertility
  No effect of atazanavir on reproduction or fertility in male and female rodents was seen at systemic drug exposures (as measured by area under the curve) up to two times those achieved in humans at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  Atazanavir did not produce teratogenic effects in rabbits with maternal dosing producing systemic drug exposure equal to (rabbits) or twice that (rats) achieved in humans at the recommended therapeutic dose. In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure twice that achieved in humans at the recommended therapeutic dose resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.

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

- Placental and breast milk passage
  It is unknown whether atazanavir crosses the placenta. Atazanavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

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

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

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

- Reproduction/fertility
  No impairment of fertility or mating was seen in rats at doses providing three to four times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No affect was seen on the development or maturation of sperm in rats at these doses.

- Teratogenicity/developmental toxicity
  Fosamprenavir was studied in rabbits at 0.8 and in rats at two times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. At these doses, the incidence of abortion was increased in rabbits, but no embryo-fetal effects were seen. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.

- Placental and breast milk passage
  It is unknown whether fosamprenavir crosses the placenta. Fosamprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

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

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

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.

- Reproduction/fertility
  No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.

- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity of indinavir in rats, rabbits or dogs. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related external, visceral or skeletal changes were seen in rabbits (fetal exposure limited, approximately 2% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1–2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

- Placental and breast milk passage
  Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In a phase I study in pregnant women and their infants (PACTG 358, see below), transplacental passage of indinavir was minimal *[79]*. Additionally, in a study of cord blood samples from 21 women treated with indinavir during pregnancy, the cord blood concentration of indinavir was below the assay limit of detection in samples from all women *[80]*. Indinavir is excreted in the milk of lactating rats at concentrations slightly above maternal levels (milk-to-plasma ratio 1.26 to 1.45); it is not known if indinavir is excreted in human milk.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study (PACTG 358) of indinavir (800 mg tid) in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants is being conducted (the infants do not receive indinavir in this study). Preliminary data are available from five women and infants *[79]*. One woman discontinued indinavir due to nausea and vomiting; adverse effects in the women included one case of moderately severe hyperbilirubinemia and one case of flank pain without renal stones, both of which resolved spontaneously and did not require drug discontinuation. Pharmacokinetic data from three women indicate that the plasma area under the curve (AUC) indinavir level was lower during pregnancy than postpartum or than observed in non-pregnant HIV-infected individuals. However, HIV RNA levels in the four women who completed the study decreased to undetectable levels (<400 copies/mL) prior to delivery and CD4 cell number and percentage significantly increased. The median gestational age of the five infants was 39 weeks (range 36–39 weeks). In a pharmacokinetic study of two pregnant HIV-infected women receiving combination therapy including indinavir (800 mg tid), a marked difference was noted between the AUC indinavir exposure between the third trimester and postpartum evaluations *[81]*. The AUC during the third trimester was reduced by 63% in one and 86% in the other woman when compared to 9–12 week postpartum evaluations in the same women. Similar reductions in maximum plasma indinavir concentrations were observed.

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

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies of lopinavir + ritonavir in animal systems are not completed. *In vitro* mutagenicity and clastogenicity screening tests are negative for both lopinavir and ritonavir.

  Carcinogenicity studies in mice and rats have been carried out for ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, a dose-dependent increase in liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately fourfold that in male humans at the recommended therapeutic dose (400 mg lopinavir/100 mg ritonavir bid). No carcinogenic effects were observed in female mice with exposures ninefold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

- Reproduction/fertility
  Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity with administration of lopinavir + ritonavir to pregnant in rats or rabbits. In rats treated with maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) were observed; drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a peri- and postnatal study in rats, a decrease in survival of pups between birth and postnatal day 21 occurred with exposures of 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1.0-fold for ritonavir of the exposures in humans at recommended therapeutic dose.

- Placental and breast milk passage
  Data on placental passage of lopinavir in animals are not available. For ritonavir, data in humans indicates 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
  No studies of lopinavir in human pregnancies have been conducted. A phase I/II safety and pharmacokinetic study of ritonavir given at therapeutic doses (600 mg bid) in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants (PACTG 354) is being conducted but complete data are not yet available; preliminary data indicate that there is minimal, if any, placental passage of ritonavir in humans.

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

- Animal carcinogenicity studies
  Nelfinavir is negative for mutagenicity and clastogenicity in *in vitro* and *in vivo* tests. However, thyroid follicular cell adenomas and carcinomas were increased over baseline in male rats receiving 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses) of nelfinavir.

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

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats and rabbits. Developmental toxicity, consisting of small increase in neonatal mortality and minor skeletal ossification delay, occurred at the highest dose in rats. In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to nelfinavir have been monitored to be able to detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nelfinavir. The prevalence of birth defects with first trimester nelfinavir exposure was 2.9% (95% confidence interval, 1.4-5.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- 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 *[82]*. Additionally, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was below the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 ug/mL) in the remaining 14 women *[80]*. Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study (PACTG 353) of nelfinavir in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants was conducted *[82]*. Nelfinavir administered at a dose of 750 mg tid produced drug exposures in the first nine pregnant HIV-infected women enrolled in the study that were variable and generally lower than those reported in non-pregnant adults for both tid and bid dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily, 1250 mg bid, which resulted in adequate levels of nelfinavir in pregnancy.

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

- Animal carcinogenicity studies
  In vitro mutagenicity and clastogenicity screening tests are negative for ritonavir. Carcinogenicity studies in mice and rats have been completed. In male mice, at levels of 50, 100 or 200 mg/kg/day, a dose-dependent increase in liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately fourfold that in male humans at the recommended therapeutic dose (400 mg lopinavir/100 mg ritonavir bid). No carcinogenic effects were observed in female mice with exposures ninefold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

- Reproduction/fertility
  No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible due to hepatic toxicity in the rodents.

- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity was observed in rats, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure).

- 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 *[83]*. In a phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal *[84]*. Additionally, in a study of cord blood samples from 6 women treated with ritonavir during pregnancy, the cord blood concentration was below the assay limit of detection in 83%, and was only 0.38 *u*g/mL in the remaining woman *[80]*. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants is being conducted, but complete data are not yet available. Preliminary data indicate minimal, if any, placental passage of ritonavir.

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

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies of saquinavir in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Administration of low doses of saquinavir to newborn rats was associated with gastrointestinal toxicity, including inflammation at the rectoanal junction and red anal fluid; mortality was seen at very high doses (1200 mg/kg/day).

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

- Placental and breast milk transfer
  Placental transfer of saquinavir in the rat and rabbit was minimal. In a phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal *[85]*. Additionally, in a study of cord blood samples from 8 women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was below the assay limit of detection in samples from all women *[80]*. Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study (PACTG 386) of saquinavir in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants was conducted. The standard adult dose of

saquinavir (1200 mg TID) was not sufficient to produce adequate drug levels in the first four pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in non-pregnant adults. Thus, the study was modified to evaluate the combination of saquinavir (800 mg) plus ritonavir (100 mg), both administered BID. This regimen was well-tolerated and achieved adequate saquinavir levels in the women *[85, 86]*.

FUSION INHIBITORS

Enfuvirtide, which requires subcutaneous administration, is the first of the fusion inhibitor class of antiretroviral drugs; these drugs inhibit binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein gp120 to the $CD4^+$ receptor induces conformational changes that enable gp120 to interact with a chemokine receptor on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the "fusion peptide" of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a "zipping" together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide is a synthetic 36 amino acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41. As a molecular mimic of the HR2 region, the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other antiretroviral drugs to treat advanced HIV infection in adults and children aged 6 years or older.

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

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

- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a m^2 basis).

- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.7 times, respectively, the adult human daily dose on a m^2 basis.

- Placental and breast milk passage
  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or from radio-labeled metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide is crossed the human placenta or is excreted in human milk.

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

MISCELLANEOUS AGENTS

Hydroxyurea is classified as FDA pregnancy category D.

Hydroxyurea is a cytotoxic and antimitotic agent that inhibits DNA synthesis and has been used for treatment of myeloproliferative disorders and sickle cell anemia. It has recently been studied for treatment of HIV disease in combination with nucleoside analogue antiretroviral agents. By inhibiting ribonucleotide reductase, it depletes the pool of deoxynucleoside triphosphates, particularly dATP, thereby potentiating the incorporation of the nucleoside analogue drugs into viral DNA and increasing their antiretroviral effect. However, the drug has significant toxicities and its role in HIV therapy is not well defined.

- Animal carcinogenicity studies and human data
  Hydroxyurea is genotoxic in a wide range of *in vitro* and *in vivo* animal test systems, causes cellular transformation to a tumorigenic phenotype, and is a transspecies carcinogen, which implies a potential carcinogenic risk to humans. Conventional long-term animal carcinogenicity studies have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg of hydroxyurea (approximately 0.6 to 1.2 times the maximum recommended human oral dose on a mg/m^2 basis) three times weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to controls.