Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

There are currently six approved nucleoside analogue reverse transcriptase inhibitors. Data are available from clinical trials in human pregnancy for zidovudine and lamivudine, while didanosine and stavudine are under study. Zalcitabine and abacavir have not been studied in pregnant women. Tenofovir disoproxil fumarate is the first acyclic nucleotide analogue reverse transcriptase inhibitor. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety; tenofovir, an acyclic nucleotide analogue drug, contains a mono-phosphate component attached to the adenine base, and hence only requires two phosphorylation steps to form the active moiety.

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

Animal carcinogenicity studies: Long-term animal carcinogenicity studies of abacavir in rodents are not completed; however, some in vitro mutagenesis and clastogenesis screening tests are positive.

Reproduction/fertility animal studies: No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg per day (about 8 times that of human therapeutic exposure).

Teratogenicity/developmental toxicity animal studies: Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve). Toxicity to the developing embryo and fetus (increased resorptions and decreased fetal body weight) occurred with abacavir administration to pregnant rodents at 500 mg/kg per day. The offspring of female rats treated with 500 mg/kg of abacavir beginning at embryo implantation and ending at weaning had an increased incidence of stillbirth and lower body weight throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

Placental and breast milk passage in animal studies: Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.

Human studies in pregnancy: No studies have been conducted with abacavir in pregnant women or neonates. Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults and have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

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

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

Reproduction/fertility animal studies: There has been no effect of didanosine on reproduction or fertility in rodents or on preimplantation mouse embryos *(14)*.

Teratogenicity/developmental toxicity animal studies: No evidence of teratogenicity or toxicity was observed with administration of high doses of didanosine to pregnant rats, mice, or rabbits.

Placental and breast milk passage in humans: Placental transfer of didanosine was limited in a phase I/II safety and pharmacokinetic study (cord-to-maternal blood ratio, 0.35-0.11) *(15)*. Didanosine is excreted in the milk of lactating rats; it is not known if didanosine is excreted in human breast milk.

Human studies in pregnancy: A phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through six weeks postpartum *(15)*. The drug was well-tolerated during pregnancy by the women and the fetuses. Preliminary analyses indicate that pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and that dose modification from the usual adult dosage is not needed.

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

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

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

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

Placental and breast milk passage in humans: Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations *(16)*. Lamivudine is excreted into human breast milk.

Human studies in pregnancy: A small phase I study in South Africa evaluated the safety and pharmacokinetics of lamivudine alone or in combination with zidovudine in 20 HIV-infected pregnant women; therapy was started at 38 weeks gestation, continued through labor, and given for one week following birth to the infants *(16)*. The drug was well-tolerated in the women at the recommended adult dose of 150 mg orally twice daily; pharmacokinetics were similar to those observed in nonpregnant adults, and no pharmacokinetic interaction with zidovudine was observed.

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

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

Animal carcinogenicity studies: Long-term animal carcinogenicity studies of stavudine in rodents are not completed; some in vitro and in vivo mutagenesis and clastogenicity tests are positive.

Reproduction/fertility animal studies: No effect of stavudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of stavudine of 100 μM and of postblastocyst development at 10 μM *(14)*.

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

Placental and breast milk passage in animals: Stavudine crosses the rat placenta in vivo and the human placenta ex vivo, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pigtailed macaques), fetal/maternal plasma concentrations were approximately 0.80 *(17)*. Stavudine is excreted into the breast milk of lactating rats.

Human studies in pregnancy: A phase I/II safety and pharmacokinetic study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332) is being conducted, but data are not yet available. In primate studies, pregnancy did not affect the pharmacokinetics of stavudine *(18)*.

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

Animal carcinogenicity studies: Long-term animal carcinogenicity studies of tenofovir DF in rodents are not completed; however, some *in vitro* mutagenesis and clastogenesis screening tests are positive.

Reproduction/fertility animal studies: Reproductive toxicity has been evaluated in rats and rabbits. Tenofovir had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day (exposure equivalent to approximately 10 times the human dose based on body surface area comparisons). However, there was an alteration of the estrous cycle in female rats administered 600 mg/kg/day of tenofovir.

Teratogenicity/developmental toxicity animal studies: No adverse effects on embryo/fetal development were seen when tenofovir was given in doses up to 450 mg/kg/day to pregnant rats and 300 mg/kg/day to pregnant rabbits. When tenofovir was administered to pregnant rats in

doses of 450-600 mg/kg/day, which are maternally toxic doses, peri- and post-natal development studies of their offspring showed reduced survival and slight delay in sexual maturation. However, there were no adverse effects on growth, development, behavior, or reproductive parameters when tenofovir was administered to pregnant animals at doses that were not associated with maternal toxicity (150 mg/kg/day).

Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose, exposure-, age- and species-specific. Abnormalities ranged from minimal decrease in bone mineral density and content (with oral dosing in rats and dogs that achieved drug exposures 6 to 10 times that achieved with therapeutic dosing in humans) to severe, pathologic osteomalacia (with subcutaneous dosing given to monkeys). Juvenile monkeys given chronic subcutaneous tenofovir at 30 mg/kg/day (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) developed osteomalacia, bone fractures, and marked hypophosphatemia. However, no clinical or radiologic bone toxicity was seen when juvenile monkeys received subcutaneous dosing of 10 mg/kg/day (exposure equivalent to 8 times the AUC achieved with therapeutic dosing in humans). Evidence of nephrotoxicity was observed in newborn and juvenile monkeys given tenofovir in doses resulting in exposures 12 to 50 times higher than the human dose based on body surface area comparisons.

Placental and breast milk passage in humans: Studies in rats have demonstrated that tenofovir is secreted in milk. Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, suggesting tenofovir does cross the placenta. There are no data on whether tenofovir crosses the placenta or is excreted in breast milk in humans.

Human studies in pregnancy: No studies of tenofovir have been conducted in pregnant women or neonates.

Zalcitabine (HIVID, ddC) is classified as FDA pregnancy category C

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

Reproduction/fertility animal studies: No effect of zalcitabine on reproduction or fertility in rodents has been seen. However, there is a dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition at a zalcitabine concentration of 100 μM; no inhibition of postblastocyst development was observed *(14)*.

Teratogenicity/developmental toxicity animal studies: Teratogenicity (hydrocephalus) occured in rats given very high doses (over 1000 times the maximally recommended human exposure) of zalcitabine. Developmental toxicity, consisting of decreased fetal weight and skeletal defects, has been seen in rodents at moderate to high zalcitabine doses. Cytotoxic effects were observed on rat fetal thymocytes at zalcitabine concentrations as low as 10 μM (approximately 100 times human therapeutic exposure).

Placental and breast milk passage in animal studies: In primate and placental perfusion studies, zalcitabine crosses the placenta (fetal-to-maternal drug ratio approximately 0.50 to 0.60)

(19). In rodents, zalcitabine concentrates in the fetal kidney and a relatively small proportion (approximately 20 percent) reaches the fetal brain. It is unknown if ddC is excreted in breast milk.

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

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

Animal carcinogenicity studies: Prolonged, continuous, high-dose zidovudine administration to adult rodents is associated with the development of nonmetastasizing vaginal squamous tumors in 13 percent of female rodents (at estimated drug concentrations three and 24 times that of human therapeutic exposure in mice and rats, respectively) *(1)*. In rodents, unmetabolized zidovudine is concentrated in urine with reflux into the vaginal vault. Therefore, vaginal tumors could be a topical effect of chronic zidovudine exposure on the vaginal mucosa. The observation that vaginal squamous cell carcinomas were observed in rodents exposed to 20 mg/mL zidovudine intravaginally is consistent with this hypothesis *(1)*. In humans, only metabolized zidovudine is excreted in the urine. No increase in tumors in other organ sites has been seen in adult rodent studies.

Two transplacental carcinogenicity studies of zidovudine were conducted in mice, with differing results. In one study, two very high daily doses of zidovudine were administered during the last third of gestation in mice *(2)*. These doses were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose given to humans (although the cumulative dose was similar to the cumulative dose received by a pregnant woman taking six months of zidovudine). In the offspring of zidovudine-exposed pregnant mice at the highest dose level followed for 12 months, a statistically significant increase in lung, liver, and female reproductive organ tumors was observed; the investigators also documented incorporation of zidovudine into the DNA of a variety of newborn mouse tissues, although this did not clearly correlate with the presence of tumors. In the second study, pregnant mice were given one of several regimens of zidovudine, at doses intended to achieve blood levels approximately threefold higher than human therapeutic exposure *(3)*. The daily doses received by the mice during gestation ranged from one-twelfth to one-fiftieth the daily doses received in the previous study. Some of the offspring also received zidovudine for varying periods of time over their lifespan. No increase in the incidence of tumors was observed in the offspring of these mice, except among those that received additional lifetime zidovudine exposure, in which vaginal tumors were again noted.

Transplacental carcinogenicity studies have not been performed for any of the other available antiretroviral drugs or combinations of drugs. In January 1997, the National Institutes of Health convened an expert panel to review these animal data *(4)*. The panel concluded that the known benefit of zidovudine in reducing vertical transmission of HIV by nearly 70 percent (7.2 versus 21.9 percent with placebo) *(5)* far outweighs the theoretical risks of transplacental carcinogenicity. The panel also concluded that infants with *in utero* exposure to zidovudine (or any other antiretroviral) should have long-term follow-up for potential adverse effects. No tumors have been observed in 727 children with *in utero* ZDV exposure followed for over 1,100 person-years *(6)*. While these data are reassuring, follow-up is still limited and needs to be continued into adulthood before it can be concluded that there is no carcinogenic risk.

Reproduction/fertility animal studies: No effect of zidovudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect on preimplantation mouse embryos can

occur, with inhibition of blastocyst and postblastocyst development at a zidovudine concentrations similar to levels achieved with human therapeutic doses *(7)*.

Teratogenicity/developmental toxicity animal studies: No evidence of teratogenicity or toxicity was observed with administration of doses up to 500 to 600 mg/kg per day of zidovudine to pregnant rats, mice or rabbits. However, marked maternal toxicity and an increase in fetal malformations were noted in rats given a zidovudine dose of 3000 mg/kg per day (near the lethal dose, and 350 times the peak human plasma concentration).

In humans, data from PACTG 076 study and the Antiretroviral Pregnancy Registry do not demonstrate an increased incidence of congenital abnormalities in infants born to women with antepartum ZDV exposure *(5, 8-10)*. In the PACTG 076 study, the incidence of minor and major congenital abnormalities were similar between zidovudine and placebo groups, and no specific pattern of defects was seen *(5, 9)*. However, definitive conclusions regarding teratogenic risk cannot be made due to the limited numbers of children that have been evaluated.

Placental and breast milk passage in humans: Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. ZDV is excreted into human breast milk.

Human studies in pregnancy: Zidovudine is well-tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg per kg body weight orally every six hours *(5, 11)*. Long-term data on the safety of *in utero* drug exposure in humans are not available for any antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. No difference in disease progression between women in PACTG 076 who received zidovudine and those who received placebo has been seen in follow-up through four years postpartum *(12)*. Infants with *in utero* zidovudine exposure followed for nearly six years have shown no significant differences from those who received placebo in immunologic, neurologic and growth parameters *(9, 13)*; follow-up of these infants is continuing.

Issues Related to Use of Nucleoside Analogue Drugs and Mitochondrial Toxicity

Nucleoside analogue drugs are known to induce mitochondrial dysfunction, as the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction *(20)*. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), ZDV and abacavir (ABC). Toxicity related to mitochondrial dysfunction has been reported in infected patients receiving long-term treatment with nucleoside analogues, and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested *(21)*. These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to nucleoside analogue drugs.

Issues in Pregnancy: Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance *(22)*.

These syndromes have similarities to the rare but life-threatening syndromes of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets (the HELLP syndrome) that occur during the third trimester of pregnancy. A number of investigators have correlated these pregnancy-related disorders with a recessively-inherited mitochondrial abnormality in the fetus/infant that results in an inability to oxidize fatty acids *(23-25)*. Since the mother would be a heterozygotic carrier of the abnormal gene, there may be an increased risk of liver toxicity due to an inability to properly oxidize both maternal and accumulating fetal fatty acids *(26)*. Additionally, animal studies show that in late gestation pregnant mice have significant reductions (25%-50%) in mitochondrial fatty acid oxidation and that exogeneously administered estradiol and progesterone can reproduce these effects *(27, 28)*; whether this can be translated to humans is unknown. However, these data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the etiology of acute fatty liver of pregnancy and HELLP syndrome, and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to nucleoside analogue drugs that is thought to be related to mitochondrial toxicity; it has been reported in infected individuals treated with nucleoside analogue drugs for long periods of time (>6 months). Initially, most cases were associated with AZT, but subsequently other nucleoside analogue drugs have been associated with the syndrome, particularly d4T. In a report from the FDA Spontaneous Adverse Event Program of 106 individuals with this syndrome (60 in patients receiving combination and 46 receiving single nucleoside analogue therapy), typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *(22)*. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients in this report were predominantly female gender and high body weight. The incidence of this syndrome may be increasing, possibly due to increased use of combination nucleoside analogue therapy or increased recognition of the syndrome. In a cohort of infected patients receiving nucleoside analogue therapy followed at Johns Hopkins University between 1989-1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *(29)*. However, in a report from a cohort of 964 HIV-infected individuals followed in France between 1997-1999 the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T *(30)*.

The frequency of this syndrome in pregnant HIV-infected women receiving nucleoside analogue treatment is unknown. In 1999, Italian researchers reported a case of severe lactic acidosis in an infected pregnant woman who was receiving d4T/3TC at the time of conception and throughout pregnancy who presented with symptoms and fetal demise at 38 weeks gestation *(31)*. Bristol-Myers Squibb has reported 3 maternal deaths due to lactic acidosis, 2 with and 1 without accompanying pancreatitis, in women who were either pregnant or postpartum and whose antepartum therapy during pregnancy included d4T and ddI in combination with other antiretroviral agents (either a protease inhibitor or nevirapine) *(32)*. All cases were in women who were receiving treatment with these agents at the time of conception and continued for the duration of pregnancy; all presented late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two cases were also associated with fetal demise.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogue treatment. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other significant disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving nucleoside

analogue drugs to be alert for early diagnosis of this syndrome. Pregnant women receiving nucleoside analogue drugs should have hepatic enzymes and electrolytes assessed more frequently during the last trimester of pregnancy and any new symptoms should be evaluated thoroughly. Additionally, because of the reports of several cases of maternal mortality secondary to lactic acidosis with prolonged use of the combination of d4T and ddI by HIV-infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analogue drug combinations have failed or caused unacceptable toxicity or side effects.

Issues with In Utero Exposure: A French group reported eight cases of uninfected infants with in utero and/or neonatal exposure to either ZDV/3TC (four infants) or ZDV alone (four infants) who developed indications of mitochondrial dysfunction after the first few months of life (30). Two of these infants developed severe neurologic disease and died (both of whom had been exposed to ZDV/3TC), three had mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities. It is important to note that an association between these findings and in utero exposure to antiretroviral drugs has not been established.

In infants followed through age 18 months in PACTG 076, the occurrence of neurologic events was rare – seizures occurred in one child exposed to ZDV and 2 exposed to placebo, and one child in each group had reported spasticity; mortality at 18 months was 1.4% in ZDV-exposed compared to 3.5% in placebo infants (9). In a large database that included 223 deaths in over 20,000 children with and without antiretroviral drug exposure who were born to HIV-infected women followed prospectively in several large cohorts in the United States, no deaths similar to those reported from France were identified (33). However, most of the infants with antiretroviral exposure had been exposed to ZDV alone and only a relatively small proportion (approximately 6%) had been exposed to ZDV/3TC. Evaluation is ongoing to determine if there is any evidence of mitochondrial dysfunction among any of the living children in these cohorts. Data have been reviewed relating to neurologic adverse events in 1,798 children that participated in PETRA, an African perinatal trial that compared three regimens of ZDV/3TC (before, during and one week postpartum; during labor and postpartum; and during labor only) to placebo for prevention of transmission. No increased risk of neurologic events was observed among children treated with ZDV/3TC compared to placebo, regardless of the intensity of treatment (34). Echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life in 382 uninfected infants born to HIV-infected women; 9% of infants had been exposed to ZDV prenatally (35). No significant differences in ventricular function were observed between infants exposed and unexposed to ZDV.

If the association of mitochondrial dysfunction and in utero antiretroviral exposure proves to be real, the development of severe or fatal mitochondrial disease in these infants appears to be extremely rare, and should be compared to the clear benefit of ZDV in reducing transmission of a fatal infection by nearly 70% (36). These data emphasize the importance of the existing Public Health Service recommendation for long-term follow-up for any child with in utero exposure to antiretroviral drugs.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine (Rescriptor) is classified as FDA pregnancy category C

Animal carcinogenicity studies: Long-term animal carcinogenicity studies with delavirdine in rodents are not completed; in vitro screening tests have been negative.

Reproduction/fertility animal studies: Delavirdine does not impair fertility in rodents. Teratogenicity/developmental toxicity animal studies: Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg per day during organogenesis caused ventricular septal defects. Exposure of rats to doses approximately five times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

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

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

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

Efavirenz (Sustiva) is FDA pregnancy category C

Animal carcinogenicity studies: Long-term animal carcinogenicity studies with efavirenz in rats and mice are not completed; in vitro screening tests have been negative.

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

Teratogenicity/developmental toxicity animal studies: Malformations were observed in three of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure). The malformations included anencephaly and unilateral anophthalmia in one; microphthalmia in another; and cleft palate in the third. Primate teratogenicity studies have not been conducted for delavirdine or nevirapine.

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

Human studies in pregnancy: No studies with efavirenz in pregnant humans are planned at this time. Because teratogenic effects were seen in primates at drug exposures similar to those representing human therapeutic exposure, pregnancy should be avoided in women receiving efavirenz.

Nevirapine (Viramune) is FDA pregnancy category C

Animal carcinogenicity studies: Long-term animal carcinogenicity studies with nevirapine in rats and mice are not completed; in vitro screening tests have been negative.

Reproduction/fertility animal studies: Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.

Teratogenicity/developmental toxicity animal studies: Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits. In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50 percent higher than human therapeutic exposure.

Placental and breast milk passage in humans: Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *(37)*. Nevirapine is excreted into human breast milk; the median concentration in four breast milk samples obtained from three women during the first week after delivery was approximately 76 percent (range 54 to 104 percent) of serum levels *(37)*.

Human studies in pregnancy: A phase I study (PACTG 250) evaluated the safety and pharmacokinetics of nevirapine, administered to infected pregnant women as a single 200 mg dose at the onset of labor and as a single 2 mg/kg dose to the infant at age 48 to 72 hours *(37)*. No adverse effects were seen in the women or the infants. Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar though somewhat more variable than in nonpregnant adults, possibly due to incomplete drug absorption associated with impaired gastrointestinal function during labor. Pharmacokinetic data on chronic antenatal nevirapine dosing in pregnant women are under study but not yet available. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life. The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovdine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14-16 weeks of life compared with zidovudine *(38)*. However, the women in this African trial were not receiving any other antiretroviral therapy. In the U.S., most infected women who know their HIV status during pregnancy receive standard ZDV prophylaxis combined with whatever antiretroviral therapy is needed for treatment of their HIV disease; it is unknown whether adding the HIVNET 012 nevirapine regimen to standard antiretroviral prophylaxis and treatment offers any additional benefit in terms of reducing perinatal transmission. A phase III perinatal trial (PACTG 316) being conducted in the United States, Europe, the Bahamas and Brazil is evaluating this regimen in combination with standard maternal antiretroviral therapy and ZDV antiretroviral therapy and ZDV prophylaxis for the prevention of perinatal HIV transmission. Selection of nevirapine-resistant virus was found at 6 weeks postpartum in both the untreated and antiretroviral-treated pregnant women who received a single dose of nevirapine in labor in HIVNET 012 and PACTG 316. In HIVNET 012, 7 of 31 women (23%) evaluated

developed genotypic resistance mutations at 6 weeks postpartum; these mutations were no longer present in 4 women studied at 13-18 months postpartum *(34, 39)*. In the antiretroviral-treated women in PACTG 316, 4 of 32 women (13%, 95% CI 4-25%) with HIV-1 RNA above 3,000 copies/mL at delivery who received nevirapine developed genotypic nevirapine resistance mutations compared to none of 38 women in the placebo arm *(36)*.

Severe, life-theatening and in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual HIV exposure (BI physician letter). These events have generally occurred during the first 12 weeks of therapy, and may present with non-specific prodromal signs or symptoms of hepatitis. This has not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. Severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV-infected individuals receiving nevirapine for treatment, usually during the first 12 weeks of therapy. This has not been reported with use of the HIVNET 012 two-dose nevirapine regimen.

PROTEASE INHIBITORS

Issues Related To 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 *(40-43)*. 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 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: 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 *(44)*. Almost 80 percent 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 *(45-47)*. To evaluate the baseline rates of adverse pregnancy outcome and risk factors for such outcomes in HIV-infected pregnant women, a meta-analysis of multiple PACTG perinatal trials and cohort studies is in progress. Preliminary analyses do not indicate an elevated risk of preterm delivery among infants born to women receiving combination antiretroviral therapy with or without protease inhibitors compared to those receiving single drug

or no antiretroviral therapy. 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 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: Long-term animal carcinogenicity studies of amprenavir in rats and mice are not completed; in vitro screening tests have been negative.

Reproduction/fertility animal studies: 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 animal studies: 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 in animals: 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.

Indinavir (Crixivan) is classified as FDA pregnancy category C

Animal carcinogenicity studies: Long-term animal carcinogenicity studies with indinavir in rats and mice are not completed; in vitro screening tests have been negative.

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

Teratogenicity/developmental toxicity animal studies: There has been no evidence of teratogenicity of indinavir in rats, rabbits or dogs. In rats, developmental toxicity manifest by 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 percent of maternal levels) or dogs (fetal exposure approximately 50 percent 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 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 in animals: 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 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 5 women and infants *(48)*. 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 2 pregnant HIV-infected women receiving combination therapy including indinavir (800 mg tid), a marked difference was noted between the AUC indinavir exposure between the third trimester and postpartum evaluations *(49)*. 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 4-fold 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 9-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

Reproduction/fertility animal studies: 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 animal studies: 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 in animals: Data on placental passage of lopinavir in animals are not available. For ritonavir, Tran placental passage has been observed in rat fetuses at mid- and late-gestation. 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: Long-term animal carcinogenicity studies of nelfinavir in rats and mice are not completed; in vitro screening tests have been negative.

Reproduction/fertility animal studies: 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 animal studies: No teratogenicity or effect on fetal development by nelfinavir has been demonstrated in rodent or rabbit studies at exposures comparable to human therapeutic exposure.

Placental and breast milk passage in animals: Whether nelfinavir crosses the placenta is unknown. 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 is being conducted, but complete data are not yet available. In preliminary data from this study, the standard adult dose of nelfinavir (750 mg tid) produced drug exposures in the first 9 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 has been modified to evaluate an increased dose of nelfinavir (1250 mg) administered bid. In infants, nelfinavir was not detectable in cord blood from 4 infants born to mothers receiving 750 mg nelfinavir tid; in one additional infant, the cord blood nelfinavir concentration was 11.7% that detected in maternal blood at delivery.

Ritonavir (Norvir) is classified as FDA pregnancy category B

Animal carcinogenicity studies: *In vitro* mutagenicity and clastogenicity screening tests are negative for ritonavir. Carcinogenicity studies in mice and rats have been completed. In male mice, at levels of 50, 100 or 200 mg/kg/day, a dose-dependent increase in liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately 4-fold that in male humans at the recommended therapeutic dose (400 mg lopinavir/100 mg ritonavir bid). No carcinogenic effects were observed in female mice with exposures 9-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

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

Teratogenicity/developmental toxicity animal studies: 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 percent of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22 percent 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 passage in animals: 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 *(50)*. 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]; Fortovase [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 animal studies: 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 per day).

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

Placental and breast milk transfer in animal studies: Placental transfer of saquinavir in the rat and rabbit was minimal. 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 is being conducted, but complete data are not yet available. In preliminary data from this study, the standard adult dose of saquinavir (1200 mg tid) was not sufficient to produce adequate drug exposure in the first 4 pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in non-pregnant adults. Therefore, the study has been modified to evaluate a dose of saquinavir 800 mg combined with ritonavir 100 mg both administered bid.

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 per kg of hydroxyurea (approximately 0.6 to 1.2 times the maximum recommended human oral dose on a mg per meter squared 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.

In humans receiving long-term hydroxyurea for myeloproliferative disorders such as polycythemia vera, secondary leukemias have been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term therapy.

Reproduction/fertility animal studies: Hydroxyurea administered to male rats at doses of 60 mg per kg per day (about 0.3 times the maximum recommended human daily dose on a mg per meter squared basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Teratogenicity/developmental toxicity animal studies: Potent teratogenic effects have been observed in all animal species tested, with defects reported in multiple organ systems *(51-57)*. Administration of hydroxyurea to pregnant rats at doses as low as 180 mg per kg per day (about 0.8 times the maximum recommended human daily dose on a mg per meter squared basis) and pregnant rabbits at 30 mg per kg per day (about 0.3 times the maximum recommended human daily dose on a mg per meter squared basis) was associated with embryotoxicity and fetal malformations. In pregnant rats administered doses ranging from 185 to 1000 mg per kg body weight, fetal defects that have been observed include central nervous system, cardiovascular, ocular, craniofacial, and skeletal anomalies, limb deformities, and diaphragmatic hernia, with the pattern of defects dependent on gestational day of exposure *(51, 54, 55)*. Exposure early in gestation was frequently associated with embryo death in a large percentage of cases. In pregnant rats, single doses of 375 mg per kg body weight or more (about 1.7 times the maximum recommended human daily dose on a mg per meter squared basis), were associated with growth retardation and impaired learning ability in their offspring. In hamsters, neural tube defects and cardiovascular abnormalities were produced after 50 mg of hydroxyurea was given intravenously *(52)*. In pregnant rhesus monkeys administered a cumulative dose greater than 500 mg per kg body weight, multiple skeletal, genitourinary, cardiac and ocular anomalies were found in their offspring *(54)*. Teratogenicity was also demonstrated in pregnant cats given a single oral dose of 50 or 100 mg per kg body weight *(53)*.

Placental and breast milk passage in animal studies: Hydroxyurea has been shown to cross the placenta in animals.

Placental and breast milk passage in humans: Hydroxyurea is excreted in human milk *(58)*.

Human studies in pregnancy: Published reports of hydroxyurea during human pregnancy include 16 women, all treated for primary hematologic illnesses (e.g., chronic myeloid leukemia, sickle cell anemia, primary thrombocytopenia) *(59)*. Doses ranged from 0.5 to 3 grams per day and 13 women had first trimester exposure. No fetal anomalies were seen and normal pregnancy outcomes were reported, except for one stillbirth with eclampsia at 26 weeks gestation and four elective pregnancy terminations.

Because of concerns raised by the significant anomalies seen in multiple animal species exposed to hydroxyurea and limited human information, as well as the uncertain role of Hydroxyurea in HIV therapy, hydroxyurea use as a component of antiretroviral regimen should be avoided during

pregnancy. Clinicians should counsel women of childbearing potential about potential risks of teratogenicity if they are treated with hydroxyurea and become pregnant, and encouraged to use effective contraception and avoid becoming pregnant while being treated with hydroxyurea.

ANTIRETROVIRAL PREGNANCY REGISTRY

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

It is strongly recommended that health care providers who are treating HIV-1-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry does not use patient names, and birth outcome follow-up is obtained by registry staff from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, 1410 Commonwealth Drive, Wilmington, NC 28403; telephone (800)-258-4263; fax (800) 800-1052.

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