Working Group performed a retrospective review of deaths occurring among children born to HIV-1 infected women and followed during 1986–1999 in five large prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of >16,000 uninfected children born to HIV-1 infected women with and without antiretroviral drug exposure *[41]*. 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.

In an African perinatal trial (PETRA) that compared three regimens of ZDV-3TC (during pregnancy starting at 36 weeks' gestation, during labor, and through 1 week postpartum; during labor and postpartum; and during labor only) with placebo for prevention of transmission, data have been reviewed relating to neurologic adverse events among 1,798 children who participated. No increased risk of neurologic events was observed among children treated with ZDV-3TC compared with placebo, regardless of the intensity of treatment *[42]*. The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort, 1,008 of whom had perinatal antiretroviral exposure. The median length of follow-up was 2.2 years (maximum, 16 years). No association of clinical manifestations suggestive of mitochondrial abnormalities was found with perinatal antiretroviral exposure. Of the 4 children with seizures in this cohort, none had perinatal antiretroviral exposure.

Finally, in a study of 382 uninfected infants born to HIV-1 infected women, echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life; 9% of infants had been exposed to ZDV prenatally *[43]*. No significant differences in ventricular function were observed between infants exposed and not exposed to ZDV.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. If this association is demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be compared against the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more *[44-46]*. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. These results 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
  In vitro screening tests for carcinogenicity have been negative. In rats, delavirdine was non-carcinogenic at all doses studied. In mice, delavirdine was associated with an increase in hepatocellular adenoma and carcinoma in both males and females and urinary bladder tumors in males at systemic exposures 0.5 to 3-fold higher than human exposure at therapeutic doses for female mice and at exposures 0.2 to 4-fold higher in male mice.

- Reproduction/fertility
  Delavirdine does not impair fertility in rodents. Teratogenicity/developmental toxicity animal studies: Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg/day during organogenesis caused ventricular septal defects. Exposure of rats to doses approximately 5 times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

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

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

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

Efavirenz (Sustiva®) is FDA pregnancy category C.

- Animal carcinogenicity studies
  In vitro genetic screening tests are negative for mutagenic or clastogenic effects of drug exposure. Long-term animal carcinogenicity studies with

efavirenz in mice and rats have been completed. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice but an increase in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas above background were found in female mice. In rats administered systemic drug exposures lower than that in humans receiving therapeutic doses, no increase in tumor incidence above background was observed in male or female rats.

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

- Teratogenicity/developmental toxicity animal studies:
  Significant central nervous system malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure) *[47]*. The malformations included anencephaly and unilateral anophthalmia in one; microphthalmia in another; and cleft palate in the third. Primate teratogenicity studies have not been conducted for the other non-nucleoside reverse transcription inhibitors, delavirdine or nevirapine.

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

- Human studies in pregnancy
  No clinical trials with efavirenz in pregnant humans are planned. In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry, birth defects were observed in 4 of 142 live births with first trimester exposure and 0 of 11 births with exposure later in pregnancy; none of the defects in the prospective report were neural tube defects (they included polydactaly; hydronephrosis; bilateral hip dislocation and umbilical hernia; and urinary obstruction secondary to duplicated right collecting system) *[48]*. However, in retrospective case reports, there are 3 cases of neural tube defects with first trimester efavirenz exposure *[49]* - a report of multiple defects including Dandy Walker CNS malformation in a fetus from a spontaneous abortion; a fetus with a neural tube defect in a pregnancy with elective termination in second trimester after the defect was diagnosed; and a published case report of myelomeningocele in a human infant born to a woman who was receiving efavirenz at the time of conception and during the first trimester *[50, 51]*. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz and be counseled about the potential risk to the fetus and need to avoid pregnancy. It should be noted that non-nucleoside reverse transcriptase inhibitors like nevirapine and efavirenz as well as the protease inhibitors may affect estrogen and/or norethindrone blood concentrations in women receiving oral contraceptives; additional or alternative contraception should be used by women using oral contraceptives who are receiving these antiretroviral agents. There are insufficient data on drug interactions with injectable hormones (depo-provera) to make recommendations regarding the need for additional contraception. Theoretically, since hormone levels are much higher with injectable than oral contraceptives, interactions with antiretroviral drugs may be less significant.

Nevirapine (Viramune®) is FDA pregnancy category C.

- Animal carcinogenicity studies
  In vitro screening tests for carcinogenicity have been negative. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats, and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses.

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

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

In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposure to nevirapine in humans have been monitored to be able to detect at least a 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 nevirapine. The prevalence of birth defects with first trimester nevirapine exposure was 2.0% (95% confidence interval, 0.7-4.7%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage
  Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *[52]*. Nevirapine is excreted into human breast milk; the median concentration in four breast milk samples obtained from three women during the first week after delivery was approximately 76% (range 54 to 104%) of serum levels *[52]*.

- 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 *[52]*. No adverse effects were seen in the women or the infants. Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar though somewhat more variable than in nonpregnant adults, possibly due to incomplete drug absorption associated with impaired gastrointestinal function during labor. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

  The safety, toxicity and pharmacokinetics of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants *[53]*. Initial dose pharmacokinetic profiles in pregnant women were similar to those seen in non-pregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by day 7 of life in 4 of 8 infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared with newborns whose mothers received only a single intrapartum nevirapine dose.

  The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14–16 weeks of life compared with zidovudine *[54]*. 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 combination antiretroviral therapy, usually including ZDV, as well as intravenous ZDV during delivery, with 6 weeks of ZDV given to their infant. A phase III perinatal trial (PACTG 316) conducted in the U.S., Europe, the Bahamas and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard antiretroviral therapy (at minimum the PACTG 076 ZDV regimen; 77% of women in the trial received combination therapy) would provide additional benefits in reducing transmission. Transmission was not significantly different between those having the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[55]*. Nevirapine resistance can be induced by a single mutation. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor *[56, 57]*. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13-18 months postpartum *[58]*. Evaluation at later time points was not done in PACTG 316.

  Severe, life-threatening, and in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual HIV exposure *[59]*. These toxicities have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women *[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]*.