Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

NUCLEOSIDE & NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

There are currently seven approved nucleoside analogue reverse transcriptase inhibitors. Data are available from clinical trials in human pregnancy for zidovudine, lamivudine, didanosine**,** and stavudine. Abacavir, emtricitabine, and zalcitabine have not been studied in pregnant women. Tenofovir disoproxil fumarate is the first 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 monophosphate 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
  Some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors as well as non-malignant hepatic and thyroid tumors were observed in female rats. The tumors were seen at doses in rodents that were 6 to 32 times higher than human exposure at therapeutic doses.

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

- Teratogenicity/developmental toxicity
  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 (AUC)). 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/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
  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
  There has been no effect of didanosine on reproduction or fertility in rodents or on preimplantation mouse embryos [1].

- Teratogenicity/developmental toxicity
  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
  Placental transfer of didanosine was limited in a phase I/II safety and pharmacokinetic study (cord-to-maternal blood ratio, 0.35–0.11) [2]. 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 6 weeks postpartum *[2]*. The drug was well-tolerated during pregnancy by the women and the fetuses. Pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents *[3-5]*; the FDA and Bristol Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see "Pregnancy and mitochondrial toxicity"). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

Emtricitabine (Emtriva®, FTC) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
Long-term carcinogenicity studies of emtricitabine in rodents are in progress. Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test) or the mouse lymphoma or mouse micronucleus assays.

- Reproduction/fertility
No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by area under the curve) approximately 60-fold higher in female mice and 140-fold higher in male mice than observed with human exposure at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
The incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice resulting in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses, or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.

- Placental and breast milk passage
It is unknown whether emtricitabine crosses the placenta or is excreted in human milk.

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

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
There appears to be no effect of lamivudine on reproduction or fertility in rodents.

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

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to lamivudine 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 lamivudine. The prevalence of birth defects with first trimester lamivudine exposure was 3.0% (95% confidence interval, 2.0-4.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage
Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations *[7]*. 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 1 week following birth to the infants *[7]*. 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% that of older children, requiring a reduced dosing regimen (4 mg/kg/day in neonates compared to 8 mg/kg/day for infants older than 3 months). There are currently no data on the pharmacokinetics of lamivudine between 2 to 6 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
  Some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive. In 2-year carcinogenicity studies in mice and rats, d4T was noncarcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

- Reproduction/fertility
  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 [1].

- Teratogenicity/developmental toxicity 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.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to lamivudine 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 stavudine. The prevalence of birth defects with first trimester lamivudine exposure was 2.2% (95% confidence interval, 0.9-4.4%) 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
  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 [8]. Stavudine is excreted into the breast milk of lactating rats.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study of combination d4T and 3TC in pregnant HIV-infected women and their infants has been conducted (PACTG 332). Both drugs were well-tolerated, with pharmacokinectics similar to those in non-pregnant adults [9]. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of d4T [10].

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents [3-5]; the FDA and Bristol Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see "Pregnancy and mitochondrial toxicity" on page 6). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

Tenofovir disoproxil fumarate [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
  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
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 rodents
at doses that were not associated with maternal toxicity
(150 mg/kg/day). Chronic exposure of fetal monkeys
to tenofovir at a high dose of 30 mg/kg (exposure
equivalent to 25 times the AUC achieved with
therapeutic dosing in humans) from days 20–150 of
gestation did not result in gross structural
abnormalities [11]. However, significantly lower fetal
circulating insulin-like growth factor (IGF)-1 (a
primary regulator of linear growth) and higher IGF
binding protein (IGFBP)-3 levels were shown and
were associated with overall body weights
approximately 13% lower than untreated controls. A
slight reduction in fetal bone porosity was also
observed. Effects on these parameters were observed
within 2 months of maternal treatment. Significant
changes in maternal monkey bone biomarkers were
noted but were primarily limited to the treatment
period and were reversible.

Continued administration of tenofovir at 30 mg/kg/day
to the infant monkey postnatally resulted in significant
growth restriction and severe bone toxicity in 25% of
eight infants and effects on bone biomarkers and
defective bone mineralization in all animals. 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
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%, demonstrating
that tenofovir does cross the placenta [12]. 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
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 [1].

▪ Teratogenicity/developmental toxicity
Teratogenicity (hydrocephalus) occured in rats given
very high doses (over 1,000 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 primate and placental perfusion studies, zalcitabine
crosses the placenta (fetal-to-maternal drug ratio
approximately 0.50 to 0.60) [13]. In rodents, zalcitabine
concentrates in the fetal kidney and a relatively small
proportion (approximately 20%) 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% of female rodents (at estimated drug concentrations 3 and 24 times that of human therapeutic exposure in mice and rats, respectively) [14]. 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 [14]. 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 [15]. 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 6 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 [16]. 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 [17]. The panel concluded that the known benefit of zidovudine in reducing vertical transmission of HIV by nearly 70% (7.2 versus 21.9% with placebo) [18] 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 [19]. 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
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 [20].

- Teratogenicity/developmental toxicity
No evidence of teratogenicity or toxicity was observed with administration of doses up to 500 to 600 mg/kg/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/day (near the lethal dose, and 350 times the peak human plasma concentration).

In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen [18, 21]. In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to zidovudine 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 zidovudine. The prevalence of birth defects with first trimester zidovudine exposure was 2.8% (95% confidence interval, 1.8-4.1%) 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
  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 6 hours *[18, 22]*. 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 4 years postpartum *[23]*. Infants with *in utero* zidovudine exposure followed for nearly 6 years have shown no significant differences from those who received placebo in immunologic, neurologic and growth parameters *[21, 24]*; 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 *[25]*. 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 *[26]*. These toxicities may be of particular concern for pregnant women and for 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 *[27]*.

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 *[28-30]*. 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 *[31]*. 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 *[32, 33]*; 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 *[27]*. 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 and 1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *[34]*. However, in a report from a cohort of 964 HIV-infected individuals followed in France between 1997 and 1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T *[35]*.

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 *[36]*. Bristol-Myers Squibb has reported three maternal deaths due to lactic acidosis, two with and one 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) *[3, 4]*. 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 study conducted in France reported that in a cohort of 1,754 uninfected infants born to HIV-1 infected women who received antiretroviral drugs during pregnancy, eight infants with in utero or neonatal exposure to either ZDV-3TC (four infants) or ZDV alone (four infants) developed indications of mitochondrial dysfunction after the first few months of life *[35]*. Two of these infants (both of whom had been exposed to ZDV-3TC) contracted severe neurologic disease and died, three had

mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities.

A further evaluation of mitochondrial toxicity was conducted in 4,392 uninfected or HIV-indeterminant children (2,644 with perinatal antiretroviral exposure) followed within the French Pediatric Cohort or identified within a France National Register developed for reporting of possible mitochondrial dysfunction in HIV-exposed children. Evidence of mitochondrial dysfunction was identified in 12 children (including the previous 8 reported cases), all of whom had perinatal antiretroviral exposure, an 18-month incidence of 0.26% *[37]*. Risk was higher among infants exposed to combination antiretroviral drugs (primarily ZDV/3TC) than ZDV alone. All children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or a significant episode of hyperlactatemia, and all had an identified deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy histology. An additional 14 children with "possible" mitochondrial dysfunction had unexplained clinical and/or laboratory findings for which mitochondrial dysfunction could be included in the differential diagnosis, although none had respiratory chain enzyme deficits or histologic abnormalities. In a separate publication, the same group reported an increased risk of simple febrile seizures during the first 18 months of life among uninfected infants with antiretroviral exposure *[38]*.

A small study quantified mitochondrial DNA in cord blood and peripheral blood leukocytes at age 1 and 2 years in HIV-exposed infants with (N=10) and without (N=20) perinatal ZDV exposure and infants born to HIV-uninfected women (N=30) *[39]*. Mitochondrial DNA quantity was lower in infants born to HIV-infected women overall compared to those born to uninfected women, and was lowest among those HIV-exposed infants with ZDV exposure compared to those without exposure. In another study, transient hyperlactatemia during the first few weeks of life was reported among 17 HIV-exposed infants with perinatal antiretroviral exposure; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up *[40]*. Thus, the clinical significance of these laboratory findings is unclear, and further studies are needed to validate these findings.

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 two exposed to placebo, and one child in each group had reported spasticity. Mortality at 18 months was 1.4% among infants given ZDV compared with 3.5% among those given placebo *[21]*. The Perinatal Safety Review

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