Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Nucleoside Reverse Transcriptase Inhibitor Drugs and Mitochondrial Toxicity (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
• The combination of stavudine and didanosine should not be prescribed during pregnancy because of reports of lactic acidosis and maternal/neonatal mortality with prolonged use in pregnancy **(AII)**.
• Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to antiretroviral (ARV) drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings **(AII)**.
• Long-term clinical follow-up is recommended for any child with *in utero* exposure to ARV drugs **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Nucleoside reverse transcriptase inhibitor (NRTI) drugs are known to induce mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.[1] The relative potency of the NRTI drugs in inhibiting mitochondrial gamma DNA polymerase *in vitro* is highest for zalcitabine, followed by didanosine, stavudine, zidovudine, lamivudine, abacavir, and tenofovir.[2] In one study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression.[3] Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with NRTI drugs and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested.[1] These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to NRTI drugs.

Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to NRTI drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected individuals treated with NRTI drugs for longer than 6 months. In a report from the Food and Drug Administration Spontaneous Adverse Event Program, typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness.[4] Metabolic acidosis with elevated serum lactate levels and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight.

During 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.[5, 6] These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in development of acute fatty liver of pregnancy and HELLP syndrome [7-10] and possibly contribute to susceptibility to antiretroviral (ARV)-associated mitochondrial toxicity. HELLP syndrome also can occur postpartum in women with severe preeclampsia.[11]

The frequency of this syndrome in pregnant HIV-infected women receiving NRTI drugs is unknown but a number of case reports of severe (1) or fatal (3) outcomes have been reported including several cases with

didanosine/stavudine used in combination during pregnancy. Nonfatal cases of lactic acidosis also have been reported in pregnant women receiving combination stavudine/didanosine.[12] Because of these reports of maternal mortality secondary to lactic acidosis with prolonged use of the combination of stavudine and didanosine by HIV-infected pregnant women, clinicians should not prescribe this ARV combination during pregnancy. Likewise, combination stavudine/didanosine also is not recommended for non-pregnant adults.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for non-pregnant individuals receiving NRTI drugs. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving NRTI drugs to be alert for early signs of this syndrome.

In addition to low platelets and elevated liver enzymes, other laboratory findings reported in HIV-infected pregnant women on ARV drugs include depletion of mtDNA in the placenta but without evidence of ultrastructural damage to placental cells. The clinical significance of reduced mtDNA in placentas exposed to ARV drugs remains unknown.[13] A recent report by Hernandez et al. assessed mitochondrial and apoptotic parameters in mononuclear cells from maternal peripheral blood and infant cord blood from 27 HIV-infected and ARV-treated pregnant women and their infants and 35 uninfected controls and their infants.[14] Reduced newborn mtDNA levels, decreased maternal and fetal mitochondrial protein synthesis, and reduced maternal glycerol-3-phosphate and complex III function were observed in HIV- and ARV-exposed mothers and infants compared with uninfected controls. Maternal mtDNA depletion was particularly seen in HIV-infected pregnant women who had cumulative exposure to NRTIs of more than 100 months, suggesting NRTI-mediated injury. Also, Jitratkosol et al. reported increased prevalence of AG/TG mtDNA mutations among HIV-infected pregnant women receiving antiretroviral therapy.[15] However, no clinical adverse outcomes were linked to these findings in either pregnant women or their infants.

In Utero *Exposure*

It has been suggested that mitochondrial dysfunction may develop in infants with *in utero* exposure to NRTI drugs. Data from a French cohort of 1,754 uninfected infants born to HIV-infected women who received ARV drugs during pregnancy identified 8 infants with *in utero* or neonatal exposure to either zidovudine/lamivudine (4) or zidovudine alone (4) who developed indications of mitochondrial dysfunction after the first few months of life.[16] Two of these infants (both exposed to zidovudine/lamivudine) contracted severe neurologic disease and died; 3 had mild-to-moderate symptoms; and 3 had no symptoms but had transient laboratory abnormalities.

In a larger cohort of 4,392 uninfected children (including the children in the previous study) followed within the French Pediatric Cohort or identified within a French National Register, the 18-month incidence of clinical symptoms of mitochondrial dysfunction was 0.26% and 0.07% for mortality.[17] All children had perinatal exposure to ARV drugs; risk was higher among infants exposed to combination ARV drugs (primarily zidovudine/lamivudine) than to zidovudine alone. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episodes of significant hyperlactatemia, and deficits in mitochondrial respiratory chain complex enzyme function on biopsy of muscle. The same group also has reported an increased risk of simple febrile seizures in the first 18 months of life and persistently lower (but clinically insignificant) neutrophil, lymphocyte, and platelet counts in infants with *in utero* exposure to NRTIs.[18, 19] More recently, in continued follow-up of the French Perinatal Cohort, researchers reported severe neurologic symptoms in the first 2 years of life as a rare event (0.3%–0.5%).[20]

Other clinical studies from the United States and Europe generally have not duplicated the French reports.[21-27] The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring in children born to HIV-infected women and followed from 1986 to 1999 in 5 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 more than 16,000 uninfected children born to HIV-infected women with and without exposure to ARV drugs.[22] However, most of the infants with exposure to ARVs had been exposed to zidovudine alone and only a relatively small proportion (approximately 6%) had been exposed to zidovudine/lamivudine.

The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort with median follow-up of 2.2 years (maximum, 16 years); 1,008 had perinatal exposure to ARV drugs.[24] No association was found between clinical manifestations suggestive of mitochondrial abnormalities and perinatal exposure to ARV drugs. Of the 4 children with seizures in this cohort, none had perinatal exposure to ARV drugs. In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified in a cohort of 1,037 uninfected infants born to HIV-infected mothers.[26] Definitive diagnosis was not available because none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to ARV drugs. In the 17 remaining children, although overall exposure to NRTIs was not associated with symptoms, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester. Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were found in stored specimens from these children, but the clinical significance of these observations remains unknown.[28, 29]

Laboratory abnormalities without clinical symptoms have been reported in infants with perinatal exposure to ARV drugs compared with unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In one study, mtDNA quantity was lower in cord and peripheral blood white cells at ages 1 and 2 years in 20 infants born to HIV-infected women compared with 30 infants born to uninfected women and was lowest in 10 HIV-exposed infants with zidovudine exposure compared with 10 without zidovudine exposure.[30] In a subsequent study, mitochondrial changes were evaluated in umbilical cord endothelial cells and cord blood from human infants and monkeys with *in utero* exposure to various NRTI-containing regimens.[31] Similar morphologic changes and mtDNA depletion were seen in the human and monkey infants. In the monkey study, mitochondrial damage demonstrated a gradient, with greatest damage with stavudine/lamivudine > zidovudine/didanosine > zidovudine/lamivudine > lamivudine. In a Canadian study of 73 ARV-exposed infants and 81 controls with blood samples during the first 8 months of life, investigators found that in the first weeks of life, blood mtDNA levels were higher and blood mitochondrial RNA levels were lower in the HIV- and ARV-exposed infants compared with infants without HIV and ARV exposure.[32]

Aldrovandi et al. reported that peripheral blood mononuclear cell mtDNA levels were lower at birth in HIV-exposed, ARV-exposed infants compared with non-HIV, non-ARV-exposed infants.[33] However, among the HIV-exposed infants, those with combination ARV drug exposure *in utero* had higher mtDNA levels than those exposed only to zidovudine *in utero*. Umbilical cord mtDNA sequence variants were 3-fold higher among HIV- and zidovudine-exposed infants compared with infants born to HIV-uninfected mothers.[34] Most recently, Jitratkosol reported blood mtDNA mutations in HIV-exposed infants and Hernandez et al. reported subclinical mitochondrial dysfunction with decreased mtDNA levels and mtDNA protein synthesis.[14, 15]

Other laboratory findings among HIV-exposed infants:

Transient hyperlactatemia during the first few weeks of life was reported in 17 HIV-exposed infants with perinatal exposure to ARV drugs; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up.[35] Similarly, the French Perinatal Cohort Study has reported asymptomatic hyperlactatemia in one-third of zidovudine-exposed newborns, which resolved following perinatal exposure to the drug.[20] Clinically asymptomatic hematologic findings have been reported by several investigators in uninfected infants with *in utero* exposure to ARV regimens in the United States and Europe,[36-38] and infants with exposure to triple-combination ARV regimens were found to be at increased risk of lowered hemoglobin compared with those with perinatal exposure to zidovudine or

zidovudine/lamivudine.[39] Similar hematologic findings of anemia have also been reported in a Botswana study. Dryden-Peterson et al. reported that 12.5% of breastfed infants of mothers on ARV drugs during pregnancy and during breastfeeding in Botswana experienced at least 1 episode of Grade 3 or Grade 4 reduced hemoglobin by age 6 months compared with 5.3% of breastfed infants exposed to zidovudine *in utero* followed by daily infant zidovudine for 6 months and 2.5% of infants who were exposed to the drug *in utero* and for 1 month post-birth and were formula fed.[40] The Botswana study group has also reported decreased birth weight and decreased weight for age and length for age in the first several months of life in infants exposed to ARV drugs.

Echocardiographic abnormalities have been reported among 136 ARV drug- and HIV-exposed uninfected infants compared with 216 HIV-exposed, uninfected infants without ARV drug exposure in the NHLBI CHAART-1 study.[41] In infants up to age 2 years, prenatal ARV exposure was associated with reduced left ventricular mass, dimension, and septal wall thickness z-scores and increased left ventricular fractional shortening and contractility compared with lack of ARV drug exposure. These findings were more prominent in female than in male infants.

The clinical significance of these differences in mtDNA, lactate levels, and hematologic and cardiac laboratory findings remains unclear. Further long-term studies are needed to validate the findings and assess whether they affect long-term growth and development of infants exposed to ARV drugs. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and must be balanced against the proven benefit of ARV prophylaxis in significantly reducing transmission of HIV from mothers to their infants.[24, 42, 43]

Development of new diagnostic techniques, including use of flow cytometry assays to screen for mitochondrial function, may lead to more accurate assessment of mitochondrial toxicity.[44] Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations emphasize the need for long-term clinical follow-up for any child with *in utero*, peripartum, or postnatal exposure to ARV drugs used for prevention of mother-to-child transmission.

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