Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants (Last updated October 26, 2016; last reviewed October 26, 2016)

Panel's Recommendation
• Children with *in utero*/neonatal exposure to antiretroviral drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction **(CIII)**.
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*

Data remain insufficient to address definitely the effect that exposure to antiretroviral (ARV) agents *in utero* might have on long-term risk of neoplasia or organ system toxicities in children; however, the balance of evidence over 2 decades, particularly with zidovudine, is reassuring. Potential toxicities require further, long-term investigation, especially as individual antenatal ARV and ARV combinations continue to evolve. Initial data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies were noted.[1,2] However, concerns remain that exposure to ARVs may have long-term effects on mitochondrial and immunologic function. Ongoing studies within the Pediatric HIV/AIDS Cohort Study (PHACS) and other HIV-exposed uninfected cohorts may help to identify the long-term risks of ARV drugs in exposed infants.

Potential Mitochondrial Toxicity

Nucleoside reverse transcriptase inhibitor (NRTI) drugs induce some degree of mitochondrial dysfunction reflecting varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mt DNA) depletion and dysfunction.[3-5] Aberrant histological morphology of mitochondria, mt DNA mutations, alterations in mt DNA levels in cord blood mononuclear cells, and even aneuploidy in cord blood cells have all been described in both non-human primates and neonates exposed *in utero* to NRTI drugs.[6-9] Reported increased and decreased alterations in mt DNA levels add further complexity to interpretation of their clinical significance; in addition, the data may be confounded by stage of maternal HIV infection and differences in laboratory assays and cell lines used.[8,10-12] One study has reported that respiratory chain mitochondrial function is subtly and transiently perturbed, with an increased incidence of abnormal newborn metabolic screen results for products of intermediary metabolism (elevated amino acids and acylcarnitines) in HIV-exposed (but uninfected) infants compared with HIV-unexposed infants.[13] The degrees to which these theoretical concerns and documented mitochondrial abnormalities are clinically relevant are unknown but are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[8,14]

Evidence of clinically apparent effects of mitochondrial toxicity is also conflicting. A low rate of hyperlactatemia (3.4%) is documented among HIV-exposed, uninfected infants born to U.S. women receiving antiretroviral therapy (ART).[15] However, earlier studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects possibly reflecting mitochondrial dysfunction including seizures, cognitive and motor delays, abnormal neuroimaging, hyperlactatemia, cardiac dysfunction, and two deaths, with abnormal mitochondrial histology noted among some HIV-uninfected infants born to HIV-infected women (who received or did not receive ARV drugs during pregnancy: 12/2,644 vs. 0/1,748, respectively, $P = 0.002$).[16,17] Further clinical studies from the United States and Europe have not duplicated these French reports.[18-24] 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 among a cohort of 1,037 HIV-exposed uninfected infants.[23] Definitive diagnosis was not possible

because none of the children had biopsies for mitochondrial function; however, 3 of the 20 children had no exposure to ARV drugs. In the 17 remaining children, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester, but overall exposure to NRTI drugs was not associated with symptoms. Some small alterations in mt DNA and oxidative phosphorylation enzyme activities were documented in stored specimens from these children, but the clinical significance of these observations remains unknown.[25,26]

Given the above data, 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. It is important that the long-term medical record of an uninfected child includes information about ARV exposure, should unusual symptoms develop later in life, or if adverse late effects of HIV or ARV exposure in uninfected children are identified in the future.[8,27,28]

Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs

Although older studies have not found an association between *in utero* ARV exposure and malignances, follow-up was limited to early childhood.[1,2,24] Animal studies have reported potential trans-placental genotoxicity of nucleoside analogue therapy in monkeys and micronucleated erythrocytes have been identified among infants with *in utero* nucleoside analogue exposure.[29,30] In an initial report from the French Perinatal Cohort in 2008, which included cross-check with the French National Cancer Registry, the incidence of cancer among 9,127 HIV-exposed uninfected children (median age 5.4 years) was not significantly different from that expected for the general population; however, the relative risk of cancer for children exposed to a didanosine/lamivudine combination was higher than that for zidovudine monotherapy.[31] An updated report from the French Perinatal Cohort described 21 cancers in 15,163 HIV-uninfected children (median age 9.9 years) exposed *in utero* to HIV and at least one NRTI drug.[32] While the total number of cases was not significantly different than expected for the general population, didanosine exposure was noted in a third of children who developed cancer, with a 5.5 hazard (95% CI, 2.1–14.4) of cancer with first trimester didanosine exposure. Continued follow-up of HIV- and ARV-exposed uninfected children is needed to evaluate the potential risk of cancer as these children age into adulthood.

Potential Immunologic Dysfunction

The potential impact of HIV exposure on the immune system of an uninfected infant is unclear. One study reported lower CD4 T lymphocyte (CD4) cell counts in HIV-exposed uninfected infants born to mothers whose viral load at the time of delivery was >1,000 copies/mL compared to HIV-exposed uninfected infants whose mothers had a viral load <50 copies/mL at the time of delivery.[33] The French Perinatal Cohort Group has reported an increased risk of serious bacterial infections with encapsulated organisms in HIV-exposed infants born to mothers with low CD4 number near the time of delivery.[34] Other data suggest that exposure to HIV *in utero* may be associated with alterations in CD4 and CD8 cell-mediated immune responses in infants to vaccines and non-specific antigens in infants.[35]

Recent data from Botswana also show higher rates of morbidity and mortality in HIV-exposed uninfected infants and children than in HIV-unexposed infants.[36-38] Further study is needed regarding the reproducibility of these data, and whether they are primarily associated with advanced maternal HIV disease.

Conclusion

Ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and infant feeding approaches include the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring of Antiretroviral Toxicity Study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. Because much of the available follow-up data to date relate to in utero exposure to antenatal zidovudine or other NRTIs alone, and most HIV-infected pregnant women currently receive ART regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug

exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning in utero exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

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