Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs

Panel’s Recommendation

- Children with in utero or neonatal exposure to antiretroviral (ARV) 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).
- It is important that the long-term medical record of a child without HIV includes information about in utero and neonatal ARV exposure (BIII).

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

Beginning in the 1990s, evolving long-term monitoring studies, outcomes studies, and other types of surveillance and research have been conducted to assess whether in utero exposure to antiretroviral (ARV) drugs may pose later risks to children’s health. These include studies of children without HIV infection born to women with HIV (e.g., the Pediatric AIDS Clinical Trial Group [PACTG] Late Outcomes Study and the Surveillance Monitoring for ART Toxicities [SMARTT] study from the Pediatric HIV/AIDS Cohort Study [PHACS]). Participation of children and their parents in observational studies provides an essential contribution to the research needed to monitor and identify long-term health outcomes from in utero HIV and ARV exposure. Available evidence does not permit definitive conclusions about whether in utero exposure to HIV and ARV agents might affect immunity, infectious morbidity, growth, cardiometabolic, neurodevelopmental, mitochondrial toxicity, or cancer outcomes from infancy through adulthood. Further, long-term investigation of potential HIV- and/or ARV-related toxicities is required, especially as new antiretroviral therapy (ART) for pregnant women with HIV evolves. It is important to include information about perinatal exposure to HIV and ARV agents in the long-term medical record of a child without HIV in the event that the child develops unusual symptoms later in life, or if adverse late effects of HIV or ARV exposure in children without HIV are identified in the future.1-3

Potential Increased Morbidity and Mortality

In general, the risks for increased morbidity and mortality are greater in infants who are HIV exposed but uninfected (HEU) than in infants who were HIV unexposed and uninfected (HUU). These differences are more pronounced in infants from low-middle income countries with fewer reports of similar findings in infants from high-income countries.4 Data from Botswana show higher rates of morbidity and mortality in infants and children who were HEU than in those who were HUU.5-7 A meta-analysis assessing the difference in all-cause mortality between infants and children who were HEU and those who were HUU, observed increased risk in those who were HEU.8 Further research is needed to reproduce these results and to determine an immunological basis for the increased susceptibility of infants and children who were HEU to invasive infections.9

Potential Immunologic Dysfunction and Infectious Morbidity

The potential long-term impact of HIV/ARV exposure on the immune system of an infant without HIV is unclear. A recent meta-analysis reported that, compared to infants who were HUU, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, in the first 6 months of life.10 The French Perinatal Cohort Group has observed an increased risk of serious bacterial infections with encapsulated organisms in HEU infants born to women with HIV with low CD4 T lymphocyte (CD4) cell counts near the time of delivery.11 Another study of HEU infants reported that those born to mothers whose viral load at delivery was >1,000 copies/mL had lower CD4 counts than those born to mothers whose viral load was <50 copies/mL at delivery.12 Other data suggest that exposure to HIV in utero may be associated with disturbances in infant CD4 and CD8 cell-mediated immune responses resulting in T-cell dysfunction, altered vaccine responses, and non-specific antigens in infants.13,14 More recent data indicate immune

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activation and proinflammatory responses are greater in infants who were HIV exposed than in those who were unexposed.15-21

**Potential Adverse Growth and Metabolic Outcomes**

Similar to data on overall morbidity and mortality in infants who were HEU, observations on the effect of *in utero* HIV/ARV exposure on infant and child growth have largely differed between low- and high-income settings.22-24 Among studies that compared growth in children who were HEU and those who were HUU, a recent Nigerian study reported compromised growth in children who were HEU, and a South African study found persistently lower weight-for-age z-scores (WAZ) over the first year of life, as well as higher rates of stunting, in those who were HEU.25,26 However, in a large Danish study of postnatal growth through 5 years of life, no significant differences in WAZ after 2 weeks of life or length-for-age z-scores after 6 months of life were noted between children who were HEU and a matched comparator group of children who were HUU.27 In addition, the PHACS SMARTT study in the United States has demonstrated above-average growth in children who were HEU compared to children in the general pediatric population.28 This positive relationship may carry potential long-term cardiometabolic risk for children from high-income settings who were HEU. PHACS SMARTT has found high rates of obesity in children and adolescents who were HEU,28 and obese children and adolescents who were HEU have a greater risk for systolic and diastolic hypertension than obese children and adolescents in the general pediatric population.28 In addition, although data have revealed early derangements in fuel utilization and intermediary metabolism in infants who were HEU in the United States and Africa, the significance of these findings on the long-term metabolic health of this population is still undetermined.30,31

**Potential Neurodevelopmental Outcomes**

Studies investigating whether the risk for poor neurodevelopmental outcomes is higher in children who were HEU than in those who were HUU have not been conclusive.32 In addition, the heterogeneity of study populations and study designs may further complicate interpretation of cumulative data. Several studies found no differences in early neurodevelopment between children who were HEU and those who were HUU, although some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.33-35 Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contribute to adverse neurodevelopmental outcomes among children who were HEU. Although worse infant neurodevelopment was observed with maternal viremia in one study,36 and with *in utero* efavirenz exposure in another,37 several studies have not identified associations between maternal ARV use and infant neurodevelopment.35,36,38-40 Recently, the PHACS SMARTT study evaluated the risk of microcephaly associated with *in utero* ARV exposure in children who were HEU and found that those with *in utero* exposure to efavirenz had a greater risk of microcephaly than those without *in utero* efavirenz exposure (see Teratogenicity). Neurodevelopmental assessments at ages 1 and 5 years demonstrated that HEU children with microcephaly had lower mean scores and a higher prevalence of neurodevelopmental impairment than HEU children without microcephaly.41,42 At present, there is no definitive evidence showing an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes, although recent studies37,41 provide data suggesting a possible association with EFV.

**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 (mtDNA) depletion and dysfunction.43-45 Aberrant histological morphology of mitochondria, mtDNA mutations, alterations in mtDNA 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.2,46-50 The degree to which these documented mitochondrial abnormalities are clinically relevant is unknown, but they are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.2,51
Evidence of clinically apparent effects of mitochondrial toxicity are also conflicting. Though 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 (12 of 2,644 infants vs. 0 of 1,748 infants with and without exposure to \textit{in utero} ARV drugs, respectively, $P = 0.002$)\textsuperscript{52,53} low rates of hyperlactatemia (3.4\%) have been documented among infants who were HEU born to women with HIV in the United States who were receiving ART during pregnancy.\textsuperscript{54} In addition, further clinical studies from the United States and Europe have not duplicated findings from the French studies.\textsuperscript{55-61} Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from children who were HEU in the United States. PACTG 219/219C trial, but the clinical significance of these observations is unknown.\textsuperscript{62,63}

Given the above data, mitochondrial dysfunction should be considered in children without HIV, but with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings.

\textbf{Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs}

Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys, and micro-nucleated erythrocytes have been identified in infants with \textit{in utero} nucleoside analogue exposure.\textsuperscript{64,65} An updated report from the French Perinatal Cohort described 21 cancers among 15,163 children without HIV (median age 9.9 years) exposed \textit{in utero} to HIV and $\geq 1$ NRTI drug.\textsuperscript{66,67} Among the NRTIs studied, didanosine (which is no longer recommended) was potentially associated with risk of cancer. In a study in the United States, there were four cancer diagnoses among 3,087 children exposed to HIV; the number of cancer cases did not differ significantly from the number of cases expected based on national reference rates.\textsuperscript{68} Continued follow-up of children who were HIV- and ARV-exposed but uninfected is needed to evaluate the potential risk of cancer as these children age into adulthood.

\textbf{Conclusion}

In the United States, ongoing evaluation of the early and late effects of \textit{in utero} exposure to ARV drugs and of 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. It is critical that studies to evaluate potential adverse effects of \textit{in utero} drug exposure continue to be supported given the fast pace at which newly developed ARV drugs are being made available to pregnant women living with HIV. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning \textit{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 defects and cancer registries to identify potential adverse outcomes of \textit{in utero} ARV drug exposure.

\textbf{References}


