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

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Panel's Recommendations
• 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 and outcomes studies, as well as ongoing 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 studies include children without HIV infection who are 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 following *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 immune function, infectious morbidity, growth, cardiometabolic health, neurodevelopment, mitochondrial function, or cancer risk 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 are HIV unexposed and uninfected (HUU). These differences are more pronounced in infants from low- and middle-income countries than in infants from high-income countries.[4] Higher rates of morbidity and mortality were observed in infants and children in Botswana who were HEU than in those who were HUU, with the strongest predictors of 24-month mortality being HEU status and formula feeding.[5,6] In a meta-analysis, all-cause mortality risk was higher in infants and children who were HEU than in those who were HUU.[7] Further research is needed to confirm these results and to elucidate an immunologic basis for the increased susceptibility of infants and children who were HEU to invasive infections.[8]

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. In a recent meta-analysis, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, compared with infants who are HUU in the first 6 months of life.[9] 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.[10] In a U.S. study, the rates of infection-related hospitalizations in the first 2 years of life were higher among infants who were HEU than in infants who were HUU.[11] A South African study reported higher

rates of lower respiratory tract and diarrheal illnesses in the first 6 months of life in breastfed infants who were HEU compared with breastfed infants who were HUU.[12] A potential association between maternal viral load at delivery and infant immunity also was documented previously. Here, infants who were HEU born to mothers with a viral load >1,000 copies/mL had lower CD4 counts than those born to mothers whose viral load was <50 copies/mL at delivery.[13] Immune phenotyping suggests that exposure to HIV *in utero* may be associated with perturbations in infant CD4 and CD8 cell-mediated immune responses, resulting in T-cell dysfunction and altered vaccine responses in infants who were HEU.[14,15] These observations have been supported by data showing increased monocyte activation and proinflammatory responses with downregulation of genes involved in neutrophil-mediated immunity in infants who were HEU compared with infants who were HUU.[16–23]

Potential Adverse Growth and Metabolic Outcomes

Similar to patterns of overall morbidity and mortality in infants who were HEU, the effect of *in utero* HIV/ARV exposure on infant and child growth largely has differed between low- and high-income settings.[24–29] Among studies that compared growth in children who were HEU with those who were HUU, a Nigerian study reported compromised growth in those who were HEU. Studies from South Africa and Malawi documented persistently lower weight-for-age z-scores (WAZ) in early childhood and higher rates of stunting in those who were HEU.[27,30,31] The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial from Zimbabwe reported a similar trend of increased stunting in infants who were HEU.[28] These changes may reflect disruption to the growth hormone axis in infants who were HEU compared with infants who were HUU.[28] 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.[32] Furthermore, the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort (PHACS) in the United States noted above-average weight in children who were HEU compared with children in the general pediatric population.[25] 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,[33] 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.[34] Although early derangements in fuel utilization and intermediary metabolism have been described in infants who were HEU in the United States and Africa, the significance of these findings on long-term metabolic health remains unclear.[35,36]

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.[37] The heterogeneity of study populations and study designs may further complicate the interpretation of conflicting results from different studies. Several studies found no differences in early neurodevelopment between children who were HEU and those who were HUU. However, some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.[38–42] Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contributed to adverse neurodevelopmental outcomes among children who were HEU. Although worse infant neurodevelopment was associated with maternal viremia in one study[43] and with *in utero* efavirenz exposure in another,[44] many studies have not identified associations between maternal ARV use and infant neurodevelopment.[40,43,45–47] In the PHACS SMARTT study, children who were HEU 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 children who were HEU with microcephaly had lower mean scores and a higher prevalence of neurodevelopmental impairment than children who were HEU without microcephaly.[48,49] At present, no definitive evidence shows an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes.[50]

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.[51–53] 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 nonhuman primates and neonates exposed *in utero* to NRTI drugs.[2,54–59] 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.[2,60]

Evidence of clinically apparent effects of mitochondrial toxicity also is conflicting. Although 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 *in utero* ARV drugs, respectively, $P = 0.002$)[61,62]—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.[63] In addition, further clinical studies from the United States and Europe did not corroborate findings from the French studies.[64–70] Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from children who were HEU in the U.S. PACTG 219/219C trial, but the clinical significance of these observations is unknown.[71,72]

Mitochondrial dysfunction should be considered in children without HIV but with perinatal exposure to ARV drugs who present with clinical findings of unknown etiology, particularly neurologic findings.

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 *in utero* nucleoside analogue exposure.[73,74] A report from the French Perinatal Cohort described 21 cancers among 15,163 children without HIV (median age 9.9 years) exposed in utero to HIV and ≥1 NRTI drug.[75,76] Among the NRTIs studied, didanosine (which **is no longer recommended**) was potentially associated with risk of cancer. In a study in the United States, four cancer diagnoses occurred 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.[77] 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.

Conclusion

In the United States, ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and of infant feeding practices is occurring in the PHACS SMARTT study, natural history studies, and HIV/AIDS surveillance conducted by state health departments, as well as the Centers for Disease Control and Prevention. It is critical that studies to evaluate potential adverse effects of *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 who have HIV. 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, the data from these confidential registries can be compared with information from birth defects and cancer registries to identify potential adverse outcomes of *in utero* ARV drug exposure.

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