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

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Panel's Recommendations
• Children with perinatal exposure to HIV and antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential metabolic dysfunction **(CIII).** • It is important that the long-term medical record of a child without HIV includes information about perinatal HIV and 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, long-term monitoring and outcomes studies, as well as ongoing surveillance and research, have been conducted to assess whether *in utero* exposure to HIV and antiretroviral (ARV) drugs may pose later risks to children's health. These studies (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]) include children without HIV infection who are born to mothers with HIV. 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. Furthermore, long-term investigation of potential HIV- and/or ARV-related toxicities is required, especially as antiretroviral therapy (ART) in the context of pregnancy 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 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.[4,5] 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.[6,7] In a meta-analysis, all-cause mortality risk was higher in infants and children who were HEU than in those who were HUU.[8] In a Canadian longitudinal cohort study from 1988 to 2015, children who were HEU had higher rates of hospitalization than children who were HUU across the lifespan, with an increased risk of hospitalization in infants who were HEU born small for gestational age and those with a detectable maternal viral load at delivery.[9] However, in a longitudinal cohort study following infants in Zambia for the first 6 months of life, there was no increased hospitalization or mortality in children who were HEU compared with children who were HUU.[10]

Potential Immunologic Dysfunction and Infectious Morbidity

The potential long-term impact of HIV/ARV exposure on the immune system of infants who are HEU is unclear. In a meta-analysis, infants who were HEU had a 50% and 70% increased risk for diarrhea and pneumonia, respectively, in the first 6 months of life compared with infants who were HUU.[11] Studies of infants in Malawi and South Africa who were HEU and HUU found higher rates of lower respiratory tract infections among infants who were HEU,[5,12] although other studies[13] in South Africa and Botswana did not document increased infectious morbidity among infants who were HEU.[14] The French Perinatal Cohort Group has observed an increased risk of serious bacterial infections with encapsulated organisms in infants who were HEU born to mothers with HIV with low CD4 T lymphocyte (CD4) cell counts near the time of delivery.[15] A retrospective study of 195,941 infants who were 90 days old or younger in a Spanish cohort from 2008 to 2017 found that infants who were HEU reported a sevenfold increased risk of group B streptococcus (GBS) infection and a 29-fold greater risk of GBS meningitis compared to those who were HUU.[16] A Malawian longitudinal cohort study of infants who were HEU and HUU found evidence of dysregulated monocyte and B-cell function, which could partly explain increased rates of invasive bacterial infections and pneumonia in infants who are HEU.[17] In the United States and Canada, rates of hospitalizations early in life have been found to be higher among infants who were HEU than infants who were HUU,[18-20] with respiratory syncytial virus and parainfluenza playing a potential role in these differences.[18,19] In South Africa, studies have reported higher rates of lower respiratory tract and diarrheal illnesses in the first 6 months of life, as well as infectious-cause hospitalizations between 1 month to 12 months of age, in infants who were HEU than infants who were HUU.[21,22] A potential association between maternal viral load at delivery and infant immunity was also documented—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.[23] Immune phenotyping suggests that exposure to HIV *in utero* may be associated with perturbations in infant CD4 and CD8 cell-mediated rather than humoral responses, resulting in T-cell dysfunction and altered vaccine responses in infants who were HEU.[19,24,25] These observations are supported by data showing increased monocyte activation and pro-inflammatory responses with downregulation of genes involved in neutrophil-mediated immunity in infants who were HEU compared with infants who were HUU.[26-32]

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.[33-42] 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, while studies from South Africa, Zambia, Malawi, and Uganda and a systematic review and large meta-analysis[43] from 1989 to 2022 of 28 studies (25 from Africa and 23 in the ART era) documented persistently lower weight-for-age z-scores (WAZ) and length-for-age z-scores (LAZ) in early childhood, as well as higher rates of stunting (length- or height-for-age z-score <−2) in those who were HEU.[36,39-41,44-47] These changes may reflect disruption to the growth hormone axis in infants who are HEU compared with infants who are HUU.[47] Maternal inflammation and immune activation among pregnancies with HIV may influence child growth.[48] A systematic review of studies investigating children who are HEU found that elevated markers of inflammation (i.e., acute phase reactants, pro-inflammatory cytokines, chemokines) and intestinal microbial translocation are associated with poor growth in infants who are HEU. Elevated markers of inflammation are also associated with adverse neurodevelopment in infants who are HEU.[49] Among studies that included only children who were HEU, a large study in Ethiopia demonstrated that maternal ART at conception was associated with higher rates of stunting in children who were HEU,[38] but another study in Malawi found no such association.[50] In the setting of universal maternal ART, Kenyan children who were HEU had similar growth trajectories as children who were HUU, and breastfeeding and maternal education improved children's height and weight, irrespective of maternal HIV infection.[51] 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 LAZ after 6 months of life were noted between children who were HEU and a matched comparator group of children who were HUU.[52] Furthermore, the PHACS SMARTT study in the United States reported above-average weight in children who were HEU compared with children in the general pediatric population.[34] 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,[53] and obese children and adolescents who were HEU have a greater risk of systolic and diastolic hypertension than obese children and adolescents in the general pediatric population.[54] However, a South African prospective birth cohort study evaluating cardiometabolic outcomes—including body composition and size, glucose metabolism, lipids, and blood pressure—did not detect notable differences between children who were HEU and HUU at 5 to 8 years of age.[55,56] 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.[57-59]

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.[60-64] 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.[64-66] However, some studies reported an increased risk for poorer neurodevelopmental outcomes in children who were HEU.[61-63,65-69] A systematic review in three studies found a higher prevalence of psychiatric disorders in children who were HEU compared to children who were HUU, which was linked to socioeconomic status, stigma, and increased psychosocial stress.[70] In Kenya, children who were HEU had significantly lower mean z-scores for global cognitive ability than children who were HUU, as well as short-term and delayed memory, attention, and processing speed, even after adjusting for child nutritional status, household food security, and orphanhood.[71] In a South African cohort study, impaired language development was seen in children who were HEU compared with children who were HUU across the preschool years.[72] In this same cohort, children who were HEU were found to have thicker prefrontal cortices than children who were HUU, which may account for their language impairment[73] Among a large cohort of 3- to 6-year-old children who were HEU from eastern/southern Africa, group-mean composite neurodevelopmental scores averaged within the low-normal range, with differences noted by country and maternal clinical and socioeconomic factors.[74] These data may reflect recent findings documenting lower caudate and total grey matter volumes in infants who were HEU than infants who were HUU in the first weeks of life. Furthermore, maternal immunosuppression was associated with reduced caudate and grey matter volumes. These findings suggest that antenatal HIV exposure may impact early structural brain development.[75]

Some studies evaluated whether maternal factors or *in utero* ARV drug exposure contributed to adverse neurodevelopmental outcomes among children who were HEU. Although delayed infant neurodevelopment was associated with maternal viremia in one study[76] and with *in utero* efavirenz exposure in another,[77] many studies have not identified associations between maternal ARV use and infant neurodevelopment.[68,76,78-80]

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 Efavirenz). Neurodevelopmental assessments at ages 1 year 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.[81,82] Presently, no definitive evidence shows an association between *in utero* exposure to specific ARV drugs and poorer neurodevelopmental outcomes.[83]

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.[84-86] Aberrant 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 neonates and young children exposed *in utero* to NRTI drugs.[2,87-89] The degree to which these documented mitochondrial abnormalities are clinically relevant is unknown, but they are outweighed significantly by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.[2,90] In addition, newer NRTIs, such as tenofovir, have not been associated with the same degree of mitochondrial toxicity as older NRTIs, such as zidovudine, lamivudine, and abacavir.[85,91,92]

Although early studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects reflecting either established or possible mitochondrial dysfunction,[93,94] further clinical studies from the United States and Europe did not corroborate findings from the French studies.[95-101] 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.[102-104] Mitochondrial dysfunction may be considered in children without HIV but with perinatal exposure to ARV drugs who present with clinical findings of unknown etiology, particularly metabolic or 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.[105,106] 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 at least one NRTI drug.[107,108] A U.S. study using state health department records of 13,617 children who were HEU and followed for a median of 9.3 years, with a maximum of 20 years, found a borderline elevated risk for brain cancer, based on six cases, and no significant increased risk for leukemia.[109] 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.[110] 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 during pregnancy with 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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