New Challenges in the Elimination of Pediatric HIV Infection: The Expanding Population of HIV-Exposed but Uninfected Children

Lynne M. Mofenson
Elizabeth Glaser Pediatric AIDS Foundation, Washington, D.C.

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The discovery that antiretroviral interventions can prevent mother-to-child human immunodeficiency virus (HIV) transmission during pregnancy, delivery, and more recently, during breastfeeding, and implementation of these interventions in low-resource as well as high-resource countries, has been one of the great success stories of the HIV epidemic. Increased global availability of combination antiretroviral therapy (ART) for HIV-infected individuals in general, and for pregnant women specifically, has dramatically decreased the number of newly infected infants from an estimated 570,000 in 1999 to 240,000 in 2013; 40% of this decline occurred between 2009 and 2013, greater than observed in the entire prior decade [1]. Progress was spurred by the 2011 United Nations Joint Programme for HIV/AIDS Global Plan for the Elimination of New HIV Infection Among Children by 2015 and Keeping Their Mothers Alive and infusion of the US President’s Emergency Plan for AIDS Relief funding to increase treatment availability in low-resource settings, including lifelong therapy for pregnant women living with HIV [2, 3]. Although the goal of a 90% decrease in new pediatric infections may not be met by the end of 2015, it is clearly within reach, with nearly 70% of the estimated 1.5 million pregnant women living with HIV in 2013 receiving antiretroviral drugs [1, 4].

One consequence of this dramatic success is that millions of infants who are now uninfected will have in utero and in some cases up to 2 years of breastfeeding exposure to both HIV and multiple antiretroviral drugs for which there are limited data on long-term safety. Thus, any health problems that might be associated with HIV and/or antiretroviral exposure in this large number of uninfected children could have important public health significance. However, there have been limited studies to date to evaluate the long-term effects of such exposures on HIV-exposed but uninfected (HEU) children, particularly in low-resource settings, where nutritional deficiencies and endemic infections are common and could exacerbate any potential adverse effects of HIV/antiretroviral drug exposure [5, 6]. In this issue of Clinical Infectious Diseases, von Mollendorf and colleagues report a significantly increased risk of invasive pneumococcal disease (IPD) and mortality among HEU children compared with HIV-unexposed young infants in South Africa [7].

A number of studies have suggested that HEU infants have an increased risk of morbidity and mortality, primarily from infectious causes, compared with children born to HIV-uninfected mothers [8–14]. Whereas the majority of studies are from the pre-ART era and low-resource settings, similar reports have been published in the ART era from higher-resource settings in Latin America and Europe [15–17]. The reasons for this increased risk are likely multifactorial. In addition to adverse social and economic factors associated with being born into an HIV-affected household, increased exposure to infectious pathogens from their HIV-infected mother or other family members, and shortened duration of breastfeeding, some data suggest that in utero exposure to HIV itself can affect the immune response in the fetus, with lasting effects into childhood [18, 19]. Increased risk of morbidity and mortality in HEU children has been associated with advanced maternal HIV disease during pregnancy, including low maternal CD4 cell count and viremia [12, 17, 20, 21].
Additionally, some studies have suggested that there may be potential adverse effects of in utero/neonatal exposure to antiretroviral drugs, ranging from increased rates of preterm delivery and low birth weight to mitochondrial, hematologic, and metabolic abnormalities [6, 18, 22].

The intrauterine period is a critical time during which fetal programming, mediated by epigenetic-induced changes in fetal gene expression, can affect the lifelong health of an individual [23]. Studies in both animal models and humans have shown that exposure to an unfavorable environment (eg, produced by maternal disease, treatments, or nutrition) in early life can result in fetal or neonatal epigenetic changes that may alter the expression of genes and lead to changes that may persist throughout life and cause increased susceptibility to disease [24, 25].

Growing evidence suggests that maternal infection with pathogens during pregnancy, including helminths, Trypanosoma cruzi, Plasmodium species, and, potentially, HIV, may affect the developing fetus independent of mother-to-child transmission of the pathogen [26]. Fetal adaptive immune responses are common in neonates exposed to maternal infection during pregnancy but who are not themselves infected. Chronic maternal infection may result in maternal inflammatory responses and/or transplacental transfer of microbial antigens or infected cells that could affect the innate immune responses in the placenta and fetus or affect transfer of maternal antibodies. This could result in alterations in immunity to unrelated pathogens, response to vaccines, or sensitization or tolerance to homologous pathogens.

A range of phenotypic and functional immunoologic differences has been reported in HEU infants compared with infants born to uninfected mothers. At birth and prior to immunization, HEU infants have been shown to have lower antibody levels to a number of pathogens compared with HIV-unexposed infants, potentially increasing vulnerability to infectious diseases early in life [27–31]. Other abnormalities that have been described include altered lymphocyte subsets; altered proinflammatory cytokine production and T-cell immune activation; skewed T-cell memory and differentiation subset distributions; increased susceptibility to T-cell apoptosis; altered dendritic cell phenotype; reduced thymic size; reduced peripheral T-cell receptor excision circles; skewed maturation of B-cell subsets; and impaired response to vaccines [18, 29, 32–36]. Most reports have not looked longitudinally at persistence of these abnormalities, although at least 1 study has suggested that these abnormalities may be transient [32].

Additionally, a number of biologic alterations have been described in HEU infants that have been potentially linked to ART exposure. Although the data are conflicting, increased rates of preterm delivery and low birth weight have been reported in infants born to mothers receiving combination ART [37, 38]. Perinatal ART exposure has been associated with subclinical abnormalities in hematologic parameters in HEU children in large European and US cohorts, which may be persistent [39–41]. Primarily subclinical alterations in mitochondrial function has been described, including abnormal mitochondrial morphology and mitochondrial DNA content, as well as rare neurologic deficits, in ART-exposed HEU infants [22, 42]. Transient disruption of fetal metabolic pathways has been suggested by the finding of abnormal newborn metabolic screens in ART-exposed HEU infants [43, 44].

Thus, limited data, primarily from high-resource settings, suggest that HIV and possibly ART exposure may be associated with immunologic and biologic abnormalities that could predispose HEU children to an increased risk of illness and mortality, particularly in the first few years of life. An accurate assessment of this risk, particularly in low-resource settings, is critical to evaluate the health needs for this expanding population of children. In this issue, von Mollendorf and colleagues have innovatively used data from a national, laboratory-based surveillance program for IPD in South Africa to evaluate IPD incidence in infants aged <1 year by HIV exposure/infection status in 2009 IPD cases reported from 2009 through 2013 [7]. More than 200 hospital-based diagnostic laboratories systematically report IPD cases of all ages to the national surveillance program, with 25 enhanced sentinel hospital sites in all 9 provinces—contributing 50% of cases—also collecting data on HIV exposure status and in-hospital outcomes. Data on HIV status were available on 92% of cases from enhanced sites. For incidence calculations in 2009 (prior to national introduction of pneumococcal conjugate vaccine [PCV]) and 2013 (after PCV introduction), they assumed a similar prevalence of HIV infection and exposure between nonenhanced sites and enhanced sites.

As would be expected, HIV-infected children had the highest risk of and mortality from IPD, even in the current ART and PCV national immunization program era. However, HEU children were twice as likely to have an IPD-associated hospitalization as were HIV-unexposed infants. HEU infants aged <6 months also had significantly increased mortality compared with unexposed infants (33.7% vs 22.4%, respectively). Other investigators have reported an increased risk of clinical failure for pneumonia therapy among HEU infants compared with unexposed infants [9, 45]. Interestingly, mortality risk in the older group (6–12 months) was reversed, being nonsignificantly higher among unexposed than HEU infants; however, the prevalence of underlying conditions predisposing to IPD and potentially to mortality (eg, asplenia, non-HIV immunocompromising illnesses, chronic diseases) was higher among older unexposed than among HEU infants (29.1% vs 19.5%, respectively).

Breastfeeding data were only available for children enrolled in a nested case-
control study, but in these data, the rate of breastfeeding in the first 4 months of life was significantly lower in HEU than unexposed children (33% vs 81%, respectively). This could have contributed to the elevated rate of IPD in HEU children [46–48]; in a study from Kenya, breastfeeding was associated with a 47% decrease in pneumonia incidence and 74% lower risk of pneumonia-related hospitalization in HEU children [49]. Additionally, HEU infants were less likely to have completed the 2-dose PCV series than were unexposed infants (24.8% vs 31.6%, respectively), which could have contributed to higher rates of IPD in the HEU infants.

The data from von Mollendorf and colleagues provide important confirmatory data regarding a continued risk of infectious diseases and mortality among HEU compared with unexposed children in the ART era, and point toward a critical need to evaluate potential interventions to reduce this risk, and need for retention and care for this growing group of children. As noted by the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children, HIV exposure is a lifelong condition that continues to impact the health of the HEU child long after the exposure has ended [19]. Studies to evaluate the long-term effects of HIV and ART exposure on HEU children and the mechanisms behind such effects are essential to our goals of increasing the survival of all children born to HIV-infected mothers.

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