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Revisiting Pneumonia and Exposure Status in Infants Born to HIV-Infected Mothers

Rasa Izadnegahdar, MPH, MD¹, Matthew P. Fox, MPH, DSc^{1,2}, Prakash Jeena, MBChB, FCP³, Shamim A. Qazi, MBBS, DCH, MSc, MD⁴, and Donald M. Thea, MSc, MD^{1,5}

¹Center for Global Health and Development, Boston University, Boston, MA, USA

²Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

³Pediatrics Department, N. Mandela School of Medicine, University of Kwazulu-Natal, Durban, South Africa

⁴Department of Maternal Newborn Child and Adolescent Health, World Health Organization

⁵Department of International Health, Boston University School of Public Health, Boston, MA, USA

Abstract

HIV-exposed uninfected infants are an increasing population. Past analyses have often categorized these infants as uninfected leading to inaccurate conclusions. We present a HIV exposure, rather than infection, based reanalysis of treatment failure among children with pneumonia to show that failure odds among HIV-exposed uninfected infants are intermediate between their unexposed and infected counterparts. Additional prospective studies aimed at better understanding this population are needed.

Keywords

HIV-exposed uninfected; pneumonia

With the successes in implementation of prevention of mother-to-child transmission programs and the wide roll-out of highly active antiretroviral therapy, infants who are born to HIV-infected mothers but do not go on to develop HIV infection are a rapidly increasing population. While there remains some persistent risk of postpartum HIV transmission following birth through breastfeeding, perinatal transmission has decreased in some areas to less than 5%¹. This suggests that in many parts of the world, an HIV-exposed uninfected (HEU) infant has already become the most common outcome of pregnancy from an HIV-infected mother.

Despite the fact that these children do not develop HIV infection, it is becoming increasingly clear that their immunologic and disease characteristics are not normal. Nonetheless, early studies of the impact of HIV infection on clinical outcomes commonly categorized HIV status into infected and uninfected, prioritizing the child's infections status over exposure status.

CORRESPONDENCE: Rasa Izadnegahdar, Center for Global Health and Development, Boston University, 801 Massachusetts Avenue, 3rd Floor, Boston, MA 02118, Tel: 1.617.480.3880, Fax: 1.617.414.1261, rizadnegahdar@gmail.com.

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One such study, published by our group in 2006, examined the association of HIV infection with clinical treatment failure among children 2-59 months of age with World Health Organization defined severe (chest indrawing) pneumonia and without maternal antiretroviral treatment². We found that 19% of HIV-infected children but only 10% of HIV-uninfected children met clinical failure criteria by day 2 of therapy. By day 14, failure rates were 32% for HIV-infected children and 21% for HIV-uninfected children. These findings translated to odds-ratios for treatment failure among HIV-infected children compared to uninfected children of 2.07 (95% confidence interval (CI): 1.07-4.00) and 1.88 (95% CI: 1.11-3.17) for day 2 and 14 respectively. When we reanalyzed the data by exposure status thereby removing exposed uninfected children from the uninfected category, results were notably different than originally presented. Compared to their infected or unexposed counterparts, HIV exposed uninfected children were younger and more likely to be hypoxic. They had similar sex distribution and immunization status, but had higher average weight for age scores (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B618>). HIV exposed uninfected children accounted for 33% of treatment failures by day 2 and 20% of treatment failures by day 14 among uninfected children. While odds ratios as per the original analysis comparing treatment failure between HIV-infected and uninfected children remained similar, those analyzed by exposure status demonstrated that exposed uninfected children have treatment failure odds that are intermediate between their unexposed and infected counterparts (table 1). Moreover, the separation of exposed uninfected children into a distinct category unmasked the larger magnitude of treatment failure odds ratios when comparing HIV infected children to HIV unexposed children.

Other studies have highlighted the importance of assessing the effects of HIV exposure rather than infection and focusing on the unique characteristics of the HIV-exposed uninfected population. These effects can be categorized into three distinct categories: 1) clinical presentation, 2) immune dysfunction, and 3) vaccination response.

Clinically, it is apparent that HIV-exposed uninfected infants have a greater propensity for illness and tend towards more severe disease compared to unexposed children. HEU infants have been shown to have significantly higher than background rates of invasive Group B Streptococcal infection and bronchiolitis^{3,4}. The demonstrated increased rate and severity of bronchiolitis infection in this group has been shown to be associated with low maternal and infant CD4 counts. Compared to HIV-unexposed infants, HEU infants have also been shown to have higher rates of hospitalization from all causes in the first year of life, with 50% of the increase attributable to lower respiratory tract infections⁵. Differences remained even when controlling for low birthweight, prematurity, missed immunizations, malnutrition and infant anemia.

Furthermore, among an age-matched population of HIV- exposed uninfected children undergoing surgery in South Africa, Karpelowsky and colleagues have shown higher rates of post-surgical complications, including systemic post-operative infection or surgical site complications, when compared to HIV-unexposed children (RR 3.8; 95% CI: 2.1-7.0)¹. These investigators note that the observed difference may be due to increased malnutrition among HEU children. An exposure-based reanalysis of a large cohort of Kenyan infants recruited from 1992 to 1998 corroborates this by demonstrating frequent rates of growth faltering among HEU infants including 29% as underweight (weight for age Z-score <-2), 18% with wasting (weight for length Z-score <-2) and 58% with stunting (length for age Z-score <-2)⁶. A study by McNally and colleagues, similar to our analysis, included an examination of treatment failure in South African children with pneumonia. In this study, unlike in our analysis, HIV status was found to have no impact on those with severe pneumonia⁷. HIV status was additionally found to have no impact on rates of tuberculosis,

bacteremia or infection with multiple organisms. However, when exclusively examining those with very severe disease, the authors were able to similarly show that HIV exposed uninfected individuals had risk of treatment failure and pediatric intensive care unit admission that were intermediate between their infected and unexposed counterparts. Interestingly, 3/9 HIV exposed uninfected children in this study were found to have *Pneumocystis jirovecii* pneumonia highlighting the effectively immunodeficient state of these children. Further research into whether HIV-exposed uninfected children are at increased risk of infection with drug-resistant organisms or HIV-associated opportunistic infections is needed. From an immunological perspective, recent investigations focusing on possible areas of immune dysfunction in HIV-exposed uninfected infants have demonstrated impacts on cellular and humoral responses. Earlier studies had demonstrated that mature lymphocyte phenotypes in a neonate can lead to a deficiency in Th1 cytokines and therefore has a limited ability to activate antigen presenting cells^{8,9}. Hygino and colleagues have built on these findings and demonstrate altered immune responsiveness in HIV-exposed uninfected infants with variable cytokine patterns that are attenuated by maternal antiretroviral therapy¹⁰. Additional studies have shown that these infants have lower CD4 counts and T-cell receptor impairment due to detrimental impacts on the thymus by *in utero* exposure to HIV glycoproteins¹¹⁻¹³. With regards to humoral immunity, Jones and colleagues have shown that at birth HEU infants have lower antibody levels specific to important pathogens including pneumococcus, pertussis, *Hemophilus influenzae* type B (Hib), and tetanus¹⁴. This is thought to be due to both lower antibody levels and poor transplacental antibody transfer among HIV-infected mothers leaving HIV exposed infants with lower doses of passively acquired protective antibodies.

Vaccination responses are also likely to be affected by HIV exposure status. These impacts, more so than clinical presentation and mechanisms of immune dysfunction, remain poorly understood. In a study of 53 HEU infants in Brazil, Abramczuk and colleagues demonstrated that the non-response rate to hepatitis B vaccination was nearly twice that of unexposed infants (6.7% vs. 3.6%) and that protective titers to diphtheria and tetanus were lower making it likely that immunity would wane faster among HEU children¹⁵. In a slightly larger study in South Africa conducted between 2009 and 2010, vaccine responses among HEU infants have been shown to be increased in the case of immunization against pertussis and pneumococcus but similar in the case of immunization against Hib and tetanus when compared to HIV unexposed infants¹⁴. One plausible hypothesis for the finding of increased response to immunization is that initially lower antibody levels among HEU infants may lead to less interference with the antigen load presented through vaccination therefore leading to a more robust response. A similarly more robust response to the first dose of vaccine was noted even in the case of Hib and tetanus but response differences subsided with subsequent doses. This indicates that maternal antibody interference may impact different vaccines to varying degrees.

A greater understanding with regards to disease presentation, immune function, and vaccine response among HIV-exposed infants who do not develop infection is urgently needed and reanalysis of key data stratified by exposure rather than infection status is an inexpensive means to quickly furthering our understanding of the issues. If the effects of *in utero* HIV exposure are as broad as has been suggested by the presented data, then several key interventions may need adjustment in order to produce optimal results and reduce the burden of illness. These could possibly include prolonging the duration of prophylactic medications such as cotrimoxazole, adding additional prophylactic coverage or adjusting the immunization schedule for HIV-exposed uninfected infants. Future prospective studies should assess the role of prophylaxis, immunization and other interventions in improving health outcomes among HIV-exposed uninfected children. Additionally, they should attempt to understand whether impairments to the immune system of exposed children are transient

or have meaningful long term consequences. In either case, it is clear that early maternal antiretroviral therapy which can improve maternal antibody levels and immune function should continue to remain a mainstay of prevention programs as its benefits extend to an increasingly prevalent population of exposed children without infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Proportions and odds ratios of treatment failure among participants with known exposure status presented by HIV infection status in Original Analysis and by HIV exposure and infection status, controlling for age, in Reanalysis.

Original Analysis	Failure by day 2	Odds Ratio (95% CI)	Failure by day 14	Odds Ratio (95% CI)
HIV-uninfected	18/284 (6.3%)	reference	45/284 (15.6%)	reference
HIV-infected	12/82 (14.6%)	2.53 (1.17-5.51)	20/82 (24.4%)	1.71 (0.94-3.11)
Reanalysis				
HIV-unexposed	12/244 (4.9%)	reference	36/244 (14.8%)	reference
HIV-exposed uninfected	6/40 (15.0%)	2.19 (0.75-2.75)	9/40 (22.5%)	1.18 (0.50-2.75)
HIV-infected	12/82 (14.6%)	3.48 (1.47-8.22)	20/82 (24.4%)	1.92 (1.02-3.59)