



Published in final edited form as:

AIDS. 2017 January 14; 31(2): 315–316. doi:10.1097/QAD.0000000000001315.

Protecting the Health of Our AIDS Free Generation – Beyond Prevention of Mother-to-Child HIV Transmission

Kathleen M. Powis, MD, MPH^{1,2,3}, Amy L Slogrove, MD⁴, and Lynne Mofenson⁵

¹Harvard T.H. Chan School of Public Health, Division of Immunology and Infectious Diseases, Boston MA

²Massachusetts General Hospital, Department of Internal Medicine and Pediatrics, Boston, MA

³Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

⁴University of Cape Town; Centre for Infectious Disease and Epidemiologic Research, School of Public Health and Medicine, Cape Town, South Africa

⁵Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC

Keywords

HIV-exposed; uninfected; children

We read with interest the meta-analysis of all-cause mortality among HIV-exposed uninfected (HEU) compared with HIV-unexposed children by Brennan et al [1]. Since 2006, World Health Organization (WHO) recommendations for preventing HIV transmission from mothers living with HIV to their children (PMTCT) have advanced from a dichotomized approach of triple antiretroviral (ARV) therapy (ART) for pregnant women with advanced HIV disease and maternal mono- or dual ARV prophylaxis solely for PMTCT [2], to the current policy embracing treatment as prevention, with lifetime ART for all HIV-infected pregnant women [3,4].

Maternal ART has exemplified the public health benefits of the HIV treatment as prevention policy, with a laudable MTCT reduction of 70% between 2000–2015; most of these infections were averted between 2010–2015 [5]. However, one consequence of this dramatic success is that HIV-exposed children who are uninfected will have been exposed to HIV and ART, with limited data on long-term outcomes. Some studies suggest that these children do not appear to be achieving equivalent health outcomes compared with children born to HIV-uninfected women within the same communities. Brennan et al quantify higher HEU mortality risk in the first two years of life based upon results from 21 studies. However, mortality is just one aspect of the health disparity; studies have reported higher rates of adverse birth outcomes such as preterm birth; differences in linear growth, metabolism, and adaptive and innate immune systems; and increased infectious morbidity [6–17].

Corresponding Author: Kathleen M. Powis, (617)643-2054; Fax (617)724-9068; kpowis@mgh.harvard.edu.

Potential conflicts of interest: No authors have a commercial or other associations that might pose a conflict of interest (e.g., pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding).

Neurodevelopment is also a concern; however, most HEU children reside in sub-Saharan Africa, where contextually relevant neurodevelopmental diagnostics are evolving and different diagnostic instruments are employed across studies, limiting comparability of findings. There is no question that some proportion of the HEU child's health and survival disparities are associated with the health of the HIV-infected mother, poverty-associated living circumstances that plague many HIV-affected households, and a legacy of unsafe formula-feeding [21–23]. However, while great strides have been achieved in PMTCT, there has been only limited systematic study of the health and neurodevelopmental implications of *in utero* ARV exposure. We need to identify ART regimens that optimize maternal health while achieving optimal pregnancy outcomes and ensuring the long term health of the HIV- and ART-exposed infant. The disparate mortality findings reported by Brennan et al, coupled with findings of health, growth, and metabolic disparities [6–11, 16,17] may jeopardize the achievement of many of the United Nations Sustainable Development Goals [19] in high HIV prevalence settings. In South Africa, where nearly 30% of all infants are HIV-exposed [20], reductions in under-5 mortality have plateaued since 2011, and the prevalence of stunting appears to be increasing [24–26]. It is possible that these concerning trends are fueled, in part, by the increasing population of HEU children.

The President's Emergency Plan for AIDS Relief (PEPFAR) has improved HIV healthcare infrastructure in its focus countries [18]. However, there is no mechanism to monitor health, neurodevelopment, and survival outcomes of HEU children into adulthood, a population growing at a rate of over 1 million annually, exceeding the population of HIV-infected children [5]. Attempts to systematically collect data on HEU children have been limited to high-resource settings with cohorts such as the Pediatric HIV/AIDS Cohort Study (PHACS) in the United States and the Adolescents and Adults Living with Perinatal HIV Cohort (AALPHI) in the United Kingdom. However, most HEU children are born in low-resource settings that are the epicenter of the global HIV epidemic and where nutritional deficiencies and endemic co-infections could exacerbate the potential effects of HIV/ART exposure. There is a critical need to conduct and pool standardized clinical and research safety data from pregnancy through the HEU child's progression into adolescence/young adulthood in both high- and low-resource settings, particularly as new maternal ARVs are introduced. Bench researchers need to partner with clinical researchers to identify biologically plausible mechanisms of HEU child health and survival disparities. A forum is needed where HEU observational and research data is presented, research gaps identified, and priorities established annually. Synergistically, this may be best accomplished by having a presence in existing international HIV research forums.

To achieve sustainable development goals, HEU children must be included in the agendas of UNAIDS, WHO and UNICEF, and settings with high HEU child prevalence need resources and infrastructure to follow these children. Otherwise, the public health success of an HIV-free generation will be overshadowed by persistently high under-five mortality and an HEU adult population that may not be able to contribute equally to the economic growth of their community or nation compared with HIV-unexposed peers.

Acknowledgments

Sources of Support: KMP receives salary support through an NIH funded career development grant (K23 HD070774)

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