Globally, more than 1 million HIV-exposed but uninfected (HEU) children were born in 2014 [1]. The number of HEU children born annually continues to rise, the predictable result of an ongoing adult HIV epidemic alongside new and effective strategies to prevent mother to child transmission (PMTCT) of HIV [1]. Since 2013, the WHO has recommended life-long universal triple antiretroviral therapy (ART) for HIV-infected pregnant and breastfeeding women (‘Option B+’), with a strong emphasis on exclusive and extended breastfeeding in most resource-limited settings including sub-Saharan Africa (SSA) [2].

Historically, breastfeeding by HIV-infected women was discouraged in PMTCT programs globally, including those in most resource-limited settings [3]. At the same time, access to ART was sharply limited, largely to those with advanced HIV disease. In this context, a substantial body of evidence accumulated over time and across countries demonstrating that HEU children were at increased risk of childhood mortality and morbidity. For example, a 2009 review encapsulated this thinking in providing an overview of these vulnerabilities [4], drawing on publications reporting HEU children to be at higher-than-expected risk of death, hospitalization and infectious diseases including pneumonia and diarrhea [4,5]. Similarly, a range of immunological abnormalities have been reported among HEU children born during this time, including altered cytokine profiles, changes in lymphocyte subsets and low levels of protective maternal IgG antibodies in early infancy [4,6].

Why should we rethink the HIV-exposed, uninfected child?

HEU children born under previous PMTCT strategies differed substantially from the ‘average,’ healthy, HIV-unexposed (HU) child by more than in utero exposure to HIV.
“Across the world, the distribution of HIV is heavily influenced by social and economic conditions within countries and communities.”

to maternal HIV. In particular, there are three critical child health concerns that require careful consideration.

• **Infant feeding**
  In the past, HEU and HU children have typically had vastly different infant feeding experiences. In an attempt to reduce the risk of vertical HIV transmission, previous PMTCT strategies included an emphasis on minimizing the HEU infant’s exposure to maternal breastmilk, incorporating policies promoting exclusive formula feeding or restricted breastfeeding with abrupt, early weaning [3]. Given the known and substantial benefits of exclusive and prolonged breastfeeding [7], it is not surprising that these infant feeding approaches were associated with significant increases in the risk of HEU child death [8], hospitalization [9] and infectious diseases including both diarrhea [8] and pneumonia [9]. The current promotion of early, exclusive and prolonged breastfeeding for HEU children, in line with global infant feeding recommendations across populations, is likely to substantially ameliorate at least some of the observed risk increases among HEU, particularly where maternal viral suppression through the use of ART minimizes the risk of breastfeeding-associated HIV transmission [2,7].

• **Maternal wellbeing**
  Maternal health is a central determinant of child health globally, regardless of HIV status. For HIV-infected mothers, the risks of maternal morbidity and mortality in the absence of early and effective ART are dramatically higher than those of uninfected mothers [10]. Maternal death increases the risk of child death roughly 25-fold, even in the absence of maternal HIV infection [11]; correspondingly, a 16-fold increased risk of death has been reported among HEU children who lost their mothers, compared with those whose mothers survived [12]. In addition, maternal HIV disease severity also predicts the mortality and morbidity risks of their uninfected children. A clear gradient exists linking maternal HIV disease severity and increased risk of child death, hospitalization, poor growth and pneumonia, even in the absence of maternal death [5,12]. In keeping with this, immunological abnormalities are more common among HEU children born to women with higher HIV viral loads and/or lower CD4 cell counts than among HEU children born to healthier women [13].

• **Socioeconomic determinants of child health**
  Across the world, the distribution of HIV is heavily influenced by social and economic conditions within countries and communities [14]. In turn, HEU and HU children may have differential exposures to broader social determinants of health, due to the uneven distribution of these factors among HIV-affected and HIV-unaffected households [14]. Children born into conditions of higher social and economic position, on average, survive longer and thrive compared with children born into poorer conditions [15]. The drivers of these differences are myriad and include household crowding, sanitation and food security, among other factors commonly reported among HIV-affected families [16]. These differences are well known in investigations of HEU child health, demonstrating that even within the same community, variations in socioeconomic situation can impact the health outcomes of HEU children compared with their HU counterparts, confounding the association between maternal HIV status and adverse HEU child health [8].

  Based on these considerations, four alternate explanations deserve consideration to understand the evidence regarding the health of the HEU child, and the differences observed over the past two decades in morbidity and mortality comparing HEU with HU children: the direct effect of *in utero* exposure to the virus, maternal morbidity or mortality, the quality and duration of breastfeeding and the broader social and economic determinants of child health. Much of the current thinking around the health of HEU children has been focused on the first of these four points, with inconsistent attention to the other factors, particularly all four factors in combination. However, it is plausible that the differences observed are more highly attributable to the latter three issues.

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**Key considerations for epidemiologic studies of HEU children**

Global policies seeking to optimize the health of all HIV-infected mothers and their children through lifelong use of ART (Option B+) with promotion of breastfeeding are being implemented across resource-limited settings including SSA [2]. With these policies, we are only now reaching a point when these alternate explanations may be distinguishable. While it is widely recognized that many questions
remain unanswered regarding the impact of Option B+ on maternal health and HIV-free child survival [2,17], we argue that the potential impact of Option B+ policies on HEU child health beyond survival is a critical but perhaps neglected component of the research agenda. The central research questions going forward need to be focused on whether HEU children are at increased risk of mortality and morbidity even under conditions of universal maternal ART with optimal breastfeeding; if yes, what further modifiable factors can be identified and lastly, what the best strategies are to address these factors and optimize the health of future HEU children.

To address these questions and obtain meaningful estimates of HEU child health risks under Option B+, three salient factors – maternal HIV disease severity, infant feeding and social determinants of health – require careful consideration in the design, analysis and reporting of both observational and interventional studies investigating the health of HEU children. From this, we identify three key issues in the design, conduct and analysis of these studies which, given the shortcomings of the existing literature, require special consideration going forward.

First, appropriate measurements of maternal HIV disease severity are essential toward determining the true effects of universal maternal ART on HEU child health outcomes. Recognition of the course of HIV disease, and how we measure disease progression, may help elucidate causal mechanisms driving HEU health. Outside of pregnancy, it is well understood that adults who initiate treatment at very low CD4 cell counts never fully recover functional immunity, even when virally suppressed [18]. Therefore, even with maternal viral suppression and adequate CD4 cell counts, functional immune dysfunction, which has the potential to influence HEU outcomes, may still be present in women who had been at advanced HIV disease stages when they initiated treatment prior to pregnancy. In turn, classifying maternal ART experience into simply receiving versus not receiving ART may lead to confounding by indication [19]. On a related point, while binary categorization of CD4 counts at historical treatment thresholds (such as 350 or 200 cells/mm$^3$) is commonplace, under policies of universal ART under Option B+ it will be increasingly important to understand how maternal HIV disease at higher CD4 counts may impact on both maternal and child outcomes over time [20].

Second, both maternal HIV disease severity and breastfeeding are likely to be major modifiers of the effect of maternal HIV infection on the health of HEU children [9,12]. Analyses of HEU child health outcomes should, therefore, ideally take place within strata of maternal disease severity and infant feeding. In addition to feeding modality, the quality of breastfeeding – at the minimum, distinguishing exclusivity and duration of breastfeeding – requires careful consideration [8]. Where significant effect modification is evident, as may be expected, stratum-specific rather than pooled estimates should be presented [20]. In turn, sample size calculations should ideally take into account the need for adequate power to obtain stratum-specific estimates with precision [20].

Third, estimating and predicting any excess health risks in HEU children requires appropriate comparison groups to understand local levels of child mortality and morbidity. In the ideal scenario, study designs should include HIV-unexposed comparator groups selected from the same source communities as HIV-exposed children, with detailed measurements of multiple social determinants of disease. Often HEU child health data are obtained from PMTCT trial cohorts (with all children under study HIV exposed) and comparative estimates of risks among HIV-unexposed children are unavailable. In some contexts, population-based child health statistics, such as those generated by the Demographic and Health Surveys Program, are available for comparison [21]. However, as survey data collection methods differ substantially from clinical trial data collection methods, such comparisons are at substantial risk of bias [20]. Moreover, HEU children are often concentrated in conditions of poverty, carrying with it multiple causes of child morbidity and mortality in addition to HIV exposure [16]. These social determinants of disease can be complex to measure and attempts to minimize confounding through reliance on analysis alone can provide misleading results.

**Conclusion & future perspective**

In summary, much of the evidence to date on the health of the HEU child – and in turn the public health discourse in this area – is rooted in an anachronistic view of the HIV epidemic and maternal and child health, particularly in SSA. Given the rapid recent changes to policies regarding maternal ART and breastfeeding [2], it is time for greater recognition that the health outcomes of HEU children are strongly related to maternal health, infant feeding and background social and...
economic conditions. That is, under policies of universal and lifelong maternal ART, ultimately HEU child health and survival is likely to depend on the same conditions child health advocates have been promoting through the last 50 years, for all children: ensuring maternal health and wellbeing, optimal nutrition including exclusive and extended breastfeeding, and improved living conditions for families [15]. Future research in this area must recognize these crucial factors, and include design elements and analytic approaches to address each specifically, as we seek to understand and optimize HEU child health going forward.

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