A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children

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**Objective:** Conduct a meta-analysis examining differential all-cause mortality rates between HIV-exposed uninfected (HEU) infants and children as compared with their HIV-unexposed uninfected (HUU) counterparts.

**Design:** Meta-analysis summarizing the difference in mortality between HEU and HHU infants and children. Reviewed studies comparing children in the two groups for all-cause mortality, in any setting, from 1994 to 2016 from six databases.

**Methods:** Meta-analyses were done estimating overall mortality comparing the two groups, stratified by duration of follow-up time from birth (0–12, 12–24 and >24 months) and by year enrollment ended in each study: less than 2002 compared with at least 2002, when single-dose nevirapine for prevention of mother-to-child transmission (PMTCT) commenced in low-income and middle-income countries.

**Results:** Included 22 studies, for a total of 29,212 study participants \( n = 8840 \) (30.3%) HEU; \( n = 20,372 \) (37.7%) HUU. Random effects models showed HEU had a more than 70% increased risk of mortality vs. HUU. Stratifying by age showed that HEU vs. HUU had a significant 60–70% increased risk of death at every age strata. There was a significant 70% increase in the risk of mortality between groups before the implementation of PMTCT, which remained after 2002 [risk ratio: 1.46; 95% confidence interval (CI): 1.14–1.87], when the availability of PMTCT services was widespread, suggesting that prenatal antiretroviral therapy, and healthier mothers, does not fully eliminate this increased risk in mortality.

**Conclusion:** We show a consistent increase risk of mortality for HEU vs. HUU infants and children. Longitudinal research is needed to elucidate underlying mechanisms, such as maternal and infant health status and breast feeding practices, which may help explain these differences in mortality.

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Introduction

The successful global implementation of programs to prevent mother-to-child transmission (PMTCT) of HIV via maternal antiretroviral provision has reduced the risk of perinatal transmission of HIV from 25–30% to approximately 2–5% [1,2]. Currently, approximately 1 million children are born to HIV-positive mothers each year [3]; assuming high uptake of PMTCT under current WHO guidelines [4], HIV-exposed but uninfected infants and children are the predominant pediatric population affected by HIV.

Though HIV-infected infants and children experience higher rates of morbidity and mortality than either population, a growing number of researchers have reported that HIV-exposed but uninfected children experience morbidity and death at rates exceeding that for HIV-unexposed uninfected (HUU) children [5–16]. This increased morbidity and mortality for HIV-exposed uninfected (HEU) children has been noted in both the pre-PMTCT and post-PMTCT eras and across various study settings [17]. The implication is that although effective PMTCT programs have curtailed rates of HIV transmission, it has not completely removed the risk of death or morbidity in HEU children compared with HUU children. Precise reasons for this disparity remain unclear, though it is likely multifactorial in nature, encompassing immunological, biological, maternal, social, behavioral and health systems factors [5–16].

Given the large numbers of children perinatally exposed to HIV each year, further analysis and examination of these trends in morbidity and mortality are warranted. The public health success of PMTCT, especially in this era of Option B+ globally [3], is remarkable. Although the numbers of new pediatric HIV infections will continue to decline as the number of pregnant women and mothers having access to effective PMTCT interventions increase, a commensurate number of resource-limited settings and region within the African continent (Southern, Eastern, Western and Central) [18]. Meta-regression was used to first assess the linear effect of time (1994–2015) on mortality by regressing the natural log of the ratio measures for mortality on the year study enrollment ended as a continuous variable (graphically displayed using a bubble plot) and then regressed the outcome on time as a dichotomous variable (pre–2002 vs. 2002 and after). As many countries included in the study did not revise their national policies and provide implementation training and support immediately following the publication of WHO PMTCT guidelines, we repeated the meta-regression with time stratified by pre-2004 and 2004 and after, allowing more follow-up time to potentially see an effect. This shift in time would also take into account the change in the guidelines to include triple therapy for PMTCT in low-income and middle-income countries (LMIC) [19].

Data analysis

Meta-analyses were performed to estimate overall all-cause mortality comparing HEU and HUU children and then stratified by duration of follow-up time from birth in 12-month intervals (0–12, 12–24 and >24 months). We also stratified by year enrollment ended in each study: pre-2002 vs. 2002 or after, when single-dose nevirapine for PMTCT commenced in most public sector clinics in resource-limited settings and region within the African continent (Southern, Eastern, Western and Central) [18].

Methods

Search strategy and selection criteria

We searched the databases PubMed, Web of Science (including Medline), Excerpta Medica Abstract Journals (EMBASE), ProQuest Dissertation & Thesis Outline, International AIDS Society (IAS) abstract archives and AIDS Conference abstract archives for articles and abstracts published between 1 January 1994 and 1 April 2016. We reviewed the references in the included articles and added any studies that met our inclusion criterion. Our search keywords can be found in Supplementary Table 1, http://links.lww.com/QAD/A956. We limited the search to human studies and articles published in English. Two reviewers out of five (M.K., R.C., L.G., J.U. and C.U.) screened all titles and abstracts to capture potentially relevant studies, and two reviewers (A.T.B. and R.B.) resolved any discrepancies between them. We included studies from any geographic location that compared mortality amongst HEU infants or children to HUU infants or children. Additional data were not obtained from study authors.

Data extraction

The primary objective of this study was to compare mortality among HEU children to that among HUU children in any setting. For each study when possible, we extracted year published, region, country, dates enrollment started and ended, date follow-up ended and total N in each cohort. For all-cause mortality, we extracted data on the number of deaths in individual studies, if available, and the total number of study participants to calculate simple proportions and corresponding 95% confidence intervals (CIs) for HEU and HUU children. When studies using Kaplan–Meier methods did not summarize the number of deaths and the number in the risk set, we estimated the number of deaths based on the mortality proportion identified using the Kaplan–Meier curve multiplied by the total number of study participants.
and the $I^2$ statistics [20]. Random effects models were used to estimate all combined mortality rates and corresponding 95% CIs using standard methods because there was evidence of high heterogeneity between studies [21].

**Sensitivity analysis**
To determine what proportion of the summary results driven by Marinda et al. which had the largest study population, we conducted a sensitivity analysis excluding this study.

**Publication bias**
An analysis of publication bias was also performed using a funnel plot and Egger’s linear regression test [21]. We used a confidence level of 0.10 to accommodate the low power of the Egger’s test to detect a departure from the null hypothesis of no bias (symmetrical funnel plot).

**Results**
A total of 2800 potentially relevant citations were identified, and 2451 remained after de-duplication (Fig. 1). Of 2451 articles, 204 studies appeared relevant and merited full text review, of which 22 studies published between 1994 and 2015 reported on all-cause mortality and were included; 21 (95.5%) from sub-Saharan Africa and one (4.5%) from Haiti (Table 1) [3,5,10,14,29–39]. The total population size of our study was 29,212 study participants ($n = 8840$ (30.3%) HEU and $n = 20,372$ (37.7%) HUU). Cohort size ranged from 17 to 12,645 children. Fourteen studies ended enrollment of children before the implementation of PMTCT in public sector in 2002, and eight ended enrollment of children between 2002 and 2015.

All estimates are summary pooled random effects estimates of mortality. The overall summary measure of association showed that HEU children had a 70% increase in all-cause mortality (risk ratio: 1.70; 95% CI: 1.30–2.22) compared with HUU children (Fig. 2). When stratifying by time since birth in 12 month intervals, results showed that HEU vs. HUU children had a statistically significant 60–70% increased risk of death at every age strata (birth to 12 months – risk ratio: 1.78, 95% CI: 1.14–2.78; 12–24 months – risk ratio: 1.58, 95% CI: 1.10–2.27 and >24 months – risk ratio: 1.70, 95% CI: 1.12–2.57) (Fig. 3).

When stratifying studies according to completion of participant enrollment in relation to the implementation of PMTCT in public sector (pre-2002 vs. 2002 or after), the relative risk of all-cause mortality was higher amongst HEU vs. HUU children before the implementation of PMTCT (pre-2002 risk ratio: 1.73; 95% CI: 1.22–2.46). This increased risk remained even after the widespread availability of PMTCT services, as shown when restricting the analysis to studies that completed study enrollment in 2002 or after (risk ratio: 1.46; 95% CI: 1.14–1.87) (Fig. 4), suggesting that PMTCT does not fully eliminate the risk of increased mortality. This finding was robust even when the cutoff was shifted to 2004 (pre-2004 risk ratio: 1.78; 95% CI: 1.30–2.44 vs. 2004 or after risk ratio: 1.37; 95% CI: 1.05–1.79), a time selected to account for delayed implementation of PMTCT in some situations. In meta-regression analyses, when regressing the log(risk ratio) against time as a continuous variable, there was a slight trend toward
Table 1. Characteristics of included studies and overall risk of mortality and risk ratios comparing HIV-exposed uninfected and HIV-unexposed uninfected for each study (n = 22).

<table>
<thead>
<tr>
<th>References</th>
<th>Year enrollment started</th>
<th>Year enrollment ended</th>
<th>Region</th>
<th>Country</th>
<th>Follow-up period (months)</th>
<th>Total N&lt;sup&gt;a&lt;/sup&gt; (HEU)</th>
<th>Overall mortality HEU, n (%)</th>
<th>Overall mortality HUU, n (%)</th>
<th>Crude risk ratio % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryder et al. [22]</td>
<td>1986</td>
<td>1987</td>
<td>SSA</td>
<td>Zaire</td>
<td>Birth to 36</td>
<td>582 (41.4)</td>
<td>60 (24.9)</td>
<td>21 (6.2)</td>
<td>4.0 (2.5–6.5)</td>
</tr>
<tr>
<td>Taha et al. [23]</td>
<td>1990</td>
<td>1992</td>
<td>SSA</td>
<td>Malawi</td>
<td>12–30</td>
<td>982 (29.6)</td>
<td>20 (6.9)</td>
<td>35 (5.1)</td>
<td>1.4 (0.8–2.3)</td>
</tr>
<tr>
<td>Berhane et al. [24]</td>
<td>1988</td>
<td>1994</td>
<td>SSA</td>
<td>Uganda</td>
<td>Birth to 24</td>
<td>375 (66.9)</td>
<td>14 (5.6)</td>
<td>2 (1.6)</td>
<td>3.6 (0.8–15.6)</td>
</tr>
<tr>
<td>Zijenah et al. [25]</td>
<td>1985</td>
<td>1994</td>
<td>SSA</td>
<td>Zimbabwe</td>
<td>Birth to 24</td>
<td>666 (46.2)</td>
<td>18 (5.8)</td>
<td>20 (5.6)</td>
<td>1.0 (0.6–1.9)</td>
</tr>
<tr>
<td>Sira et al. [26]</td>
<td>1995</td>
<td>1995</td>
<td>SSA</td>
<td>Rwanda</td>
<td>Birth to 60</td>
<td>449 (34.1)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Jean et al. [27]</td>
<td>1991</td>
<td>1995</td>
<td>SSA</td>
<td>Caribbean</td>
<td>Haiti</td>
<td>Birth to 24</td>
<td>139 (36.7)</td>
<td>3 (5.9)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Taha et al. [28]</td>
<td>1995</td>
<td>1995</td>
<td>SSA</td>
<td>Malawi</td>
<td>12–30</td>
<td>547 (80.3)</td>
<td>18 (4.1)</td>
<td>4 (3.7)</td>
<td>1.1 (0.4–3.2)</td>
</tr>
<tr>
<td>Taha et al. [10]</td>
<td>1995</td>
<td>1995</td>
<td>SSA</td>
<td>Malawi</td>
<td>Birth to 30</td>
<td>618 (80.7)</td>
<td>31 (6.2)</td>
<td>8 (6.7)</td>
<td>0.9 (0.4–1.9)</td>
</tr>
<tr>
<td>Ota et al. [29]</td>
<td>1993</td>
<td>1995</td>
<td>SSA</td>
<td>Malawi</td>
<td>Birth to 18</td>
<td>774 (42.1)</td>
<td>25 (7.7)</td>
<td>27 (6.0)</td>
<td>1.3 (0.8–2.2)</td>
</tr>
<tr>
<td>Schim van der Loeff et al. [30]</td>
<td>1993</td>
<td>1997</td>
<td>SSA</td>
<td>Gambia</td>
<td>Birth to 18</td>
<td>512 (12.5)</td>
<td>10 (15.6)</td>
<td>40 (8.9)</td>
<td>1.8 (0.9–3.3)</td>
</tr>
<tr>
<td>Brahmbhatt et al. [14]</td>
<td>1994</td>
<td>1998</td>
<td>SSA</td>
<td>Uganda</td>
<td>Birth to 24</td>
<td>3452 (7.8)</td>
<td>41 (15.2)</td>
<td>380 (11.9)</td>
<td>1.3 (0.9–1.7)</td>
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<tr>
<td>Marinda et al. [3]</td>
<td>1997</td>
<td>2000</td>
<td>SSA</td>
<td>Zimbabwe</td>
<td>Birth to 24</td>
<td>12645 (24.8)</td>
<td>288 (9.2)</td>
<td>276 (2.9)</td>
<td>3.2 (2.7–3.7)</td>
</tr>
<tr>
<td>Jeena et al. [31]</td>
<td>1998</td>
<td>2000</td>
<td>SSA</td>
<td>South Africa</td>
<td>12–24</td>
<td>284 (14.1)</td>
<td>1 (2.5)</td>
<td>1 (0.4)</td>
<td>6.1 (0.4–95.6)</td>
</tr>
<tr>
<td>Shapira et al. [4]</td>
<td>2001</td>
<td>2001</td>
<td>SSA</td>
<td>Swaziland</td>
<td>Birth to 24</td>
<td>671 (79.6)</td>
<td>36 (6.7)</td>
<td>2 (1.5)</td>
<td>4.6 (1.1–18.9)</td>
</tr>
<tr>
<td>Luabea et al. [32]</td>
<td>2000</td>
<td>2002</td>
<td>SSA</td>
<td>South Africa</td>
<td>Birth to 12</td>
<td>341 (45.2)</td>
<td>2 (1.3)</td>
<td>2 (1.1)</td>
<td>1.2 (0.2–8.5)</td>
</tr>
<tr>
<td>Sutcliffe et al. [33]</td>
<td>2003</td>
<td>2003</td>
<td>SSA</td>
<td>Zambia</td>
<td>Birth to 36</td>
<td>148 (64.9)</td>
<td>5 (5.2)</td>
<td>3 (5.8)</td>
<td>0.9 (0.2–3.6)</td>
</tr>
<tr>
<td>Chilongozi et al. [34]</td>
<td>2001</td>
<td>2003</td>
<td>SSA</td>
<td>Malawi, Tanzania, Zambia</td>
<td>Birth to 12</td>
<td>1456 (18.1)</td>
<td>8 (3.0)</td>
<td>18 (1.5)</td>
<td>2.0 (0.9–4.6)</td>
</tr>
<tr>
<td>Kurewa et al. [35]</td>
<td>2001</td>
<td>2005</td>
<td>SSA</td>
<td>Zambia</td>
<td>Birth to 60</td>
<td>865 (34.0)</td>
<td>34 (11.6)</td>
<td>41 (7.2)</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Arinaitwe et al. [36]</td>
<td>2003</td>
<td>2006</td>
<td>SSA</td>
<td>Uganda</td>
<td>Birth to 24</td>
<td>292 (66.1)</td>
<td>6 (3.1)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Rollins et al. [37]</td>
<td>2007</td>
<td>2008</td>
<td>SSA</td>
<td>South Africa</td>
<td>Birth to 12</td>
<td>2091 (44.8)</td>
<td>30 (13.2)</td>
<td>29 (2.5)</td>
<td>1.3 (0.8–2.1)</td>
</tr>
<tr>
<td>Dimbulasindhe et al. [38]</td>
<td>2009</td>
<td>2011</td>
<td>SSA</td>
<td>South Africa</td>
<td>Birth to 12</td>
<td>17 (35.3)</td>
<td>3 (50.0)</td>
<td>3 (27.3)</td>
<td>1.8 (0.5–6.4)</td>
</tr>
<tr>
<td>Von Mollendorf et al. [39]</td>
<td>2009</td>
<td>2011</td>
<td>SSA</td>
<td>South Africa</td>
<td>Birth to 12</td>
<td>403 (43.4)</td>
<td>59 (33.7)</td>
<td>51 (22.4)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
</tbody>
</table>

HEU, HIV-exposed uninfected; HUU, HIV-unexposed uninfected; SSA, sub-Saharan Africa.

*Total N is for HEU and HUU study participants, excluded HIV infected infants.

Sensitivity analysis
To determine what proportion of the summary results were driven by Marinda et al. which had the largest study population (n = 12,345; 44.7% of all the meta-analysis study participants), we conducted a sensitivity analysis.

Publication bias
The funnel plot and nonsignificant Egger’s test (P = 0.187) show little evidence of asymmetry suggesting little to no publication bias (Supplementary Fig. 3, http://links.lww.com/QAD/A956).

Discussion
To our knowledge, this is one of the first meta-analyses of the literature showing an increased risk of mortality in HEU children compared with HUU children in LMICs, spanning different contexts and eras of maternal antiretroviral therapy and PMTCT. The increased risks of mortality for perinatally HIV-infected infants and children has been well described compared with uninfected infants and children [40], but in the current era of worldwide Option B+ for PMTCT, HEU children are a critical population. Our results show that, overall, HEU children compared with HUU children had a 70% increase in the risk of mortality.

The impact of PMTCT programs over the last 14 years is a major public health success, and it is essential that the expansion of antiretroviral prevention and treatment programs remain a global health priority [3]. However, our results show that HEU children are at higher risk of death at least within the first 2 years of life, compared with HUU children. The precise reason for this difference in mortality is unknown, but is likely multifactorial, and may include unrecognized coinfections (e.g. pneumonia, diarrhea or malaria) in the HEU children, impact of HIV on maternal health status (e.g. high viral load, poor immunological phenomena) during pregnancy, increased risk of preterm and or low birth weight outcomes for HIV-positive women [41,42], poorer maternal health or maternal death postnatally impacting the quality of infant care.
care, or corresponding lower socioeconomic status for children born into households with an HIV-infected mother [43]. Although decreased transplacental antibody transfer from HIV-infected mothers has been demonstrated [44], the fact that the increased risk of mortality for HEU children persists to 2 years postnatally suggests that this cannot be the sole explanation for the mortality difference observed, though it may contribute to a higher mortality risk for exposed uninfected infants in the first 6 months of life. In addition, a number of immunological effects in the children of HIV-infected mothers have been noted, including increased immune activation factors in infants associated with high maternal viral load [45–48]. Few studies describe immunological changes in HIV-exposed infected and HEU children demonstrating HIV-specific immune responses in setting of maternal HIV, though the number of these studies is small [49,50]. It remains to be shown whether HIV-specific immune responses are persistent in HEU infants in this current era of complete maternal viral suppression with combination antiretroviral therapy for PMTCT [38]. In addition, decreased adaptive immunity, in the form of decreased antibody response to standard childhood immunizations, has been found in HEU children, which may account for some differences in mortality [51,52]. The decreased vaccine responses in HEU children is consistent with possible persistent immunological effects that may differentially impact or skew immune responses in the long term for HEU children as result of in-utero HIV exposure [51,52].

No studies have reported on nonbiological risk factors, such as social or environmental conditions, that might contribute to this difference in mortality. One possibility is that HIV-infected mothers may be sicker or more likely to be deceased (along with their male partner), than non-HIV infected mothers and therefore may be less able to provide care. None of the studies reported here provided such data. Such differences in maternal health status could also account for differences in breastfeeding practices.

Fig. 2. Forest plot of risk ratios for mortality comparing HIV-exposed uninfected to HIV-unexposed uninfected children for all studies (n = 22).
between HIV-positive and HIV-negative mothers. As breastfeeding occurs after in-utero HIV exposure it is an effect modifier of the relationship between HIV exposure and all-cause mortality. Previous research has established that breastfeeding is protective against all-cause mortality for all children, and is the recommended feeding modality for all mothers, including those with HIV, in LMICs [51,52]. Breast-feeding can result in mother-to-child transmission of HIV and subsequent HIV-associated mortality, but a shorter duration of breast-feeding (or no breast-feeding at all) by HIV-infected mothers increases mortality from common childhood illnesses [5,6,14,52–57]. However, previous research has shown that when breastfeeding patterns are similar, mortality in HEU...
infants is still higher than infants born to HIV-uninfected mothers [5,6,14,52].

In resource-rich settings, both monotherapy [58–60] and combination (two or more drugs) [51,61,62] antiretroviral therapy have been used since the mid-1990s to decrease the risk of transmission of the HIV virus from mother to infant (in utero, during labor and delivery, and while breastfeeding) and also improve maternal health status allowing women to live longer to care for their offspring [19]. Antiretroviral therapy in the form of single-dose nevirapine for PMTCT use was introduced in resource-limited settings in 2002 [18] and combination therapy in 2004 [19]. Our results show that HEU compared with HUU children are at higher risk of death before the implementation of single-dose nevirapine for PMTCT in most resource-limited settings since 2002. However, it is important to note that PMTCT scale-up across resource-limited settings (and even within the same country) was not instantaneous, and therefore this cutoff of 2002 is somewhat arbitrary. Even after we moved the cutoff to 2004 to allow time for the slow uptake of PMTCT at the national level and for the shift to the implementation of triple therapy, we saw similar all-cause mortality estimates.

Given that this meta-analysis reflects over a 20-year time span (1994–2015), it is important to note that there has been a substantial overall decrease in global child mortality over the same time period [63]. However, given the overall decrease in childhood mortality observed in the past 20 years, we would then expect to see a decrease in mortality in HIV-exposed children as well. This suggests that the higher mortality in HEU compared with HUU children is not due to the effects of HIV infection itself but rather to other factors that are associated with being born to a mother who is infected with HIV.
see an overall smaller effect size over time, with the assumption that childhood mortality would similarly decline in both HEU and HUU populations over the same time period.

Our results should be considered alongside their limitations. First, as with any systematic review, there is the possibility of incomplete retrieval or abstraction of data; due to either human error or those studies, primary outcome was not mortality. However, we used the most complete and comprehensive publically available literature in which most major and well conducted studies should be reported. We also used two independent reviewers for cross reference and error checking. Second, we did not obtain raw data from study investigators for pooled estimation of mortality; we used only those studies that reported appropriate simple proportions or included Kaplan–Meier curves in their data presentation. Third, there was also substantial heterogeneity among the studies. Despite this heterogeneity, we felt it was important to pool the existing data to estimate mortality probability as these data provide a more robust estimate than any single study alone. Fourth, given the smaller number of studies in the postantiretroviral therapy PMTCT era, it is not possible for us to know how much of this effect on child mortality is mediated by maternal antiretroviral therapy (and, subsequently, improved maternal or paternal health status). Fifth, the majority of studies included in our analysis were conducted in an era when antiretrovirals therapy was not available for pregnant women. As such, our inability to account for differences in maternal health status and maternal mortality between HIV-positive and HIV-negative women could result in an overestimate of our results. Maternal health status, in relation to when HIV exposure in the infant occurs, could confound or modify the association, whereas maternal mortality is an effect modifier as it occurs after HIV exposure in the infant. Sixth, we were unable to account for breastfeeding practices as an effect modifier in our study. With the exception of Shapiro et al. [6], whose entire study population for the analysis was the arm of The Mashi Study randomized to 6 months exclusive breastfeeding, and Rollins et al. [37] who classified breastfeeding according to WHO definitions as exclusive, predominant or never breastfed, no other study clearly defined breastfeeding practices. As such, our results could be overestimating the association between HIV-exposure and all-cause mortality. However, as the previous research has shown [5,6,14,52], even when controlling for breastfeeding HEU infants and children remain at higher risk of mortality compared with their HIV unexposed counterparts.

Conclusion
We show that there is a consistently observed increased risk of all-cause mortality for HEU infants and children compared with HUU infants and children. The mechanisms for this difference will require carefully conceived prospective cohorts to determine which of the several potential biological or environmental factors is partly or wholly responsible. With the great success of PMTCT, change in breastfeeding practices and HIV-infected adults living longer because of antiretroviral therapy, the population of HEU infants is increasing, highlighting the importance and need to understand the long-term health outcomes in this population. Understanding the causes of increased mortality in HIV-exposed, but uninfected, children will help countries strengthen the capacity to provide quality long-term services for this population. These efforts should ideally be complementary to national and international efforts to improve overall child survival as HEU children are still at risk from major childhood diseases such as pneumonia, diarrhea and malnutrition.

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Conflicts of interest
There are no conflicts of interest.

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