Systematic Review

Mortality risk and associated factors in HIV-exposed, uninfected children

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Abstract   OBJECTIVE With increasing maternal antiretroviral treatment (ART), the number of children newly infected with HIV has declined. However, the possible increased mortality in the large number of HIV-exposed, uninfected (HEU) children may be of concern. We quantified mortality risks among HEU children and reviewed associated factors.

METHODS Systematic search of electronic databases (PubMed, Scopus). We included all studies reporting mortality of HEU children to age 60 months and associated factors. Relative risk of mortality between HEU and HIV-unexposed, uninfected (HUU) children was extracted where relevant. Inverse variance methods were used to adjust for study size. Random-effects models were fitted to obtain pooled estimates.

RESULTS A total of 14 studies were included in the meta-analysis and 13 in the review of associated factors. The pooled cumulative mortality in HEU children was 5.5% (95% CI: 4.0–7.2; I^2 = 94%) at 12 months (11 studies) and 11.0% (95% CI: 7.6–15.0; I^2 = 93%) at 24 months (four studies). The pooled risk ratios for the mortality in HEU children compared to HUU children in the same setting were 1.9 (95% CI: 0.9–3.8; I^2 = 93%) at 12 months (four studies) and 2.4 (95% CI: 1.1–5.1; I^2 = 93%) at 24 months (three studies).

CONCLUSION Compared to HUU children, mortality risk in HEU children was about double at both age points, although the association was not statistically significant at 12 months. Interpretation of the pooled estimates is confounded by considerable heterogeneity between studies. Further research is needed to characterise the impact of maternal death and breastfeeding on the survival of HEU infants in the context of maternal ART, where current evidence is limited.

keywords HIV, mortality, infant, child, risk factor, meta-analysis

Introduction

With increasing availability of lifelong antiretroviral treatment (ART) globally, risk of mother-to-child transmission (MTCT) of HIV has dramatically changed over the past decades. When antiretroviral drugs are available as prophylaxis, overall HIV transmission can be reduced to <5% at cessation of breastfeeding [1]. UNAIDS reported that many low- and middle-income countries had achieved at least 80% coverage of services to prevent HIV transmission to children by December 2009, with global coverage reaching 53% [1]. In this context, the number of children newly infected with HIV was reported to be 220 000 [190 000–260 000] in 2014, a 48% reduction from 2002 in the highest-burden countries

[2]. The risk of MTCT has been reduced to virtually zero in high-income countries. While serious challenges remain in resource-limited countries to ensure better access to and coverage of ART, elimination of MTCT is now on the global agenda [3]. With fewer infants and children becoming infected with HIV each year, attention has been given to the health and survival of children born to HIV-infected mothers who are themselves not HIV-infected (HIV-exposed, uninfected children, hereafter HEU children).

Studies have suggested increased mortality risks in this group, mostly based on data from a time when antiretroviral drugs (ARVs) were not available [4–6]. Mortality estimates are scarce in settings where maternal ARV or lifetime ART is available. Different factors are associated

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with vulnerability of HEU children: (i) altered caregiving practices when the mother was unwell or died [4]; (ii) infant feeding practices aimed at preventing HIV transmission through breastfeeding, including early weaning and inappropriate use of breastmilk substitutes [6–8]; (iii) increased exposure to comorbidities secondary to living in HIV-affected households [9]; and (iv) sociodemographic and geographic factors related to the HIV status of the mother [4]. In addition to such external and potentially modifiable risk factors, inherent vulnerability of HEU children has also been reported. Exposure to HIV is associated with immunological alterations among HEU children that may put them at higher risk of certain infections, especially in the absence of or with shorter breastfeeding [10, 11]. Poor weight gain and linear growth as well as high incidence of invasive group B streptococcal infections among HEU children have been reported in Europe and the United States, suggesting adverse impacts of HIV exposure and altered immunological response in this group [12, 13]. A study from South Africa demonstrated that at birth, HEU infants had lower antibody responses to certain pathogens than children born to HIV-uninfected women (HIV-unexposed, uninfected children, hereafter HUU children) [14].

Building on available literature, the present study aims to analyse the risk of increased mortality among HEU children. Given the scarcity of data reporting mortality in HEU children *vs.* HUU children living in the same communities with similar access to health services, we firstly aim to generate the pooled mortality rates of HEU children specifically. Where data are available, the pooled relative risk of mortality of HEU children compared to HUU children is estimated. Finally, we aim to systematically compile and describe factors, which might influence the risk of death of HEU children to better understand the drivers of their mortality risk.

Method

Search methods for identification of studies

Electronic searches were conducted in PubMed and Scopus for studies published between 2004 and 2015 with the following keywords: 'HIV'; 'Mortality'; and 'Child' or 'Infant'. The search strategy used in the databases is shown in Appendix S1. We restricted our search to studies published from 2004 for three main reasons. Firstly, a pooled analysis was published on the same topic in 2004 which comprehensively covered the data available at that time and reported mortality in HEU infants in sub-Saharan Africa [15]. Secondly, ART roll-out has began in earnest in most African settings from 2004,

which was expected to bring positive impact on both maternal and infant survival. Finally, background mortality decreased significantly over the past decade under the Millennium Development Goals aiming at reducing child mortality. There were no restrictions on the type of studies. Published data from all regions were eligible. Language was limited to English or French. Relevance of studies was assessed by screening their title and abstract. Retained articles were subject to full-text reviews. References of selected articles were screened manually to identify additional studies.

Inclusion and exclusion criteria

Studies were included if they reported mortality of infants and/or children born to mothers who tested HIV positive but where the infants/children themselves tested HIV negative without seroconversion during follow-up. Primary outcome was all-cause mortality in HEU children at any time point between birth and 60 months of age. Relative risk of mortality between HEU and HUU children was also sought as primary outcome when studies included HIV-unexposed children as a control group. Studies reporting case-specific mortality estimates were excluded. Studies not reporting raw data were also excluded from the analysis as they did not allow calculation of mortality estimates or relative risk with 95% confidence interval. In certain cases, authors of studies were contacted to obtain data. For qualitative analysis, studies were included if they reported factors associated with mortality risks of HEU children.

Statistical analysis

Primary data regarding the sample size, the number of death and the total number of time at risk observed (where incidence density is reported) were extracted as raw numbers. Inverse variance methods were used to adjust for study size, and random-effects models were fitted [16]. Pooled mortality rates of HEU children at different time points, calculated as the number of deaths observed divided by the number of live births, and risk ratios of mortality between HEU and HUU children, where available, were presented using a forest plot along with the weight of each study in the pooled effect size. The degree of between-study heterogeneity was assessed using I^2 statistics [17]. When high heterogeneity was observed ($I^2 > 75\%$), the source of heterogeneity was explored narratively by assessing exposure to factors that can influence the risk of mortality. Sensitivity analyses were performed to explore the effect of studies with high risk of classification bias on the pooled estimates. The analyses were performed with REVIEW MANAGER version

5.3 and METAXL version 2.2. We also undertook a narrative qualitative analysis on factors possibly associated with mortality of HEU children. The quality of the studies included in the meta-analysis was assessed using the GRADEpro GDT (http://www.guidelinedevelopment.org/).

This review was conducted in accordance with PRISMA guidelines.

Results

Characteristics of included studies

As shown in Figure 1, 1867 articles were identified through electronic searches, of which 59 were retained for full-text review. A total of 35 studies were excluded for different reasons but mainly due to absence of disaggregated data on children's HIV status. Hand searches of the reference lists of the remaining 24 articles identified seven additional studies. Of 31 articles deemed relevant at this stage, we finally retained 14 for meta-analysis by excluding six articles which did not report mortality estimates in HEU infants and a further 11 articles for different reasons: one study reporting a case fatality rate for invasive pneumococcal disease [18], one pooled analysis [15], four studies as their mortality rates were generated with particular inclusion criteria (e.g. conditional on survival to 9 months) [7, 19, 20, 21], one study including children who were too old for the purpose of the study [22], and four studies because they reported the mortality at 4, 9 and 18 months from birth [8, 23–25]. We were unable to make use of all the data retrieved from individual studies as they estimated mortality risks at diverse time points. In this study, we chose the mortality estimates at 3, 6, 12 and 24 months from birth as these time points were used by most studies. The 14 included and 11 excluded articles are listed in Appendix S2. For qualitative analysis, we retained 13 articles with information on associated factors.

Thirteen of the 14 studies included in the meta-analysis were undertaken in sub-Saharan Africa, and one was conducted in India. All included studies were observational in nature: eight were nested within clinical trials [26–33] and six were based on cohort data [4–6, 34–36]. The majority were undertaken before the widespread use of maternal ART. Table 1 summarises the characteristics of the studies included in the meta-analysis.

Quality of evidence of the included studies

As shown in Table 2, we assessed the quality of evidence in the included studies according to different outcomes.

As all studies were observational, the quality of evidence was deemed low [37]. As for the cumulative mortality in HEU infants at 3 months, the overall quality of six studies was downgraded to very low due to high inconsistency in study results and variability in study population in terms of access to maternal ART, breastfeeding and infant cotrimoxazole. For the same reasons, the overall quality of the studies that included 6-, 12- and 24-month estimates was assessed as very low. For these three estimates, downgrading was also related to the risk of classification bias in the studies of Marinda *et al.* [4] and Wei *et al.* [35].

For the relative risk of mortality between HEU and HUU children at both 12 and 24 months, the quality of evidence was also downgraded to very low because of high inconsistency in study results, the risk of classification bias in Marinda's study and the small number of studies included in the generation of pooled estimates.

Mortality estimates of HEU children (Meta-analysis)

As Figure 2a shows, pooled mortality in HEU infants at 3 months of age was 2.0% [95% confidence interval (CI): 1.5–2.7], based on 131 deaths among 5967 HEU infants from six studies [26, 29, 33, 34]. The studies of Becquet *et al.* and Kafulafula *et al.* show estimates from two independent studies conducted in the same setting with no overlaps in the study populations (Ditrame & Ditrame Plus for Becquet *et al.* [34] and PEPI trial & NVAZ trial for Kafulafula *et al.* [29]). The reported mortality varied from 1.0% to 2.6%. A substantial difference was observed in the duration of breastfeeding; about half the infants in Ditrame Plus in Cote d'Ivoire had short-term breastfeeding (a median of 4 months), whereas most infants in NVAZ in Malawi were breastfed for longer than 12 months. All six studies were conducted before the availability of lifelong maternal ART. In Bork's study (Kesho Bora), a randomised controlled trial in Burkina Faso, Kenya and South Africa, half of the women received triple ARVs until breastfeeding cessation after 6 months. As indicated by the value of I^2, 60% of variability between studies cannot be explained by chance. Duration of breastfeeding might explain to a certain extent the inconsistency in reported mortality rates; however, we were unable to undertake subgroup analyses because the information on the median duration of breastfeeding was not available in all studies.

Seven studies reported the mortality in HEU infants at 6 months of age [4, 6, 26, 29, 34], which differed significantly between studies: from 2.4% in the study of Bork *et al.* to 6.0% in that of Marinda *et al.* There was no coverage of lifelong maternal ART when these studies
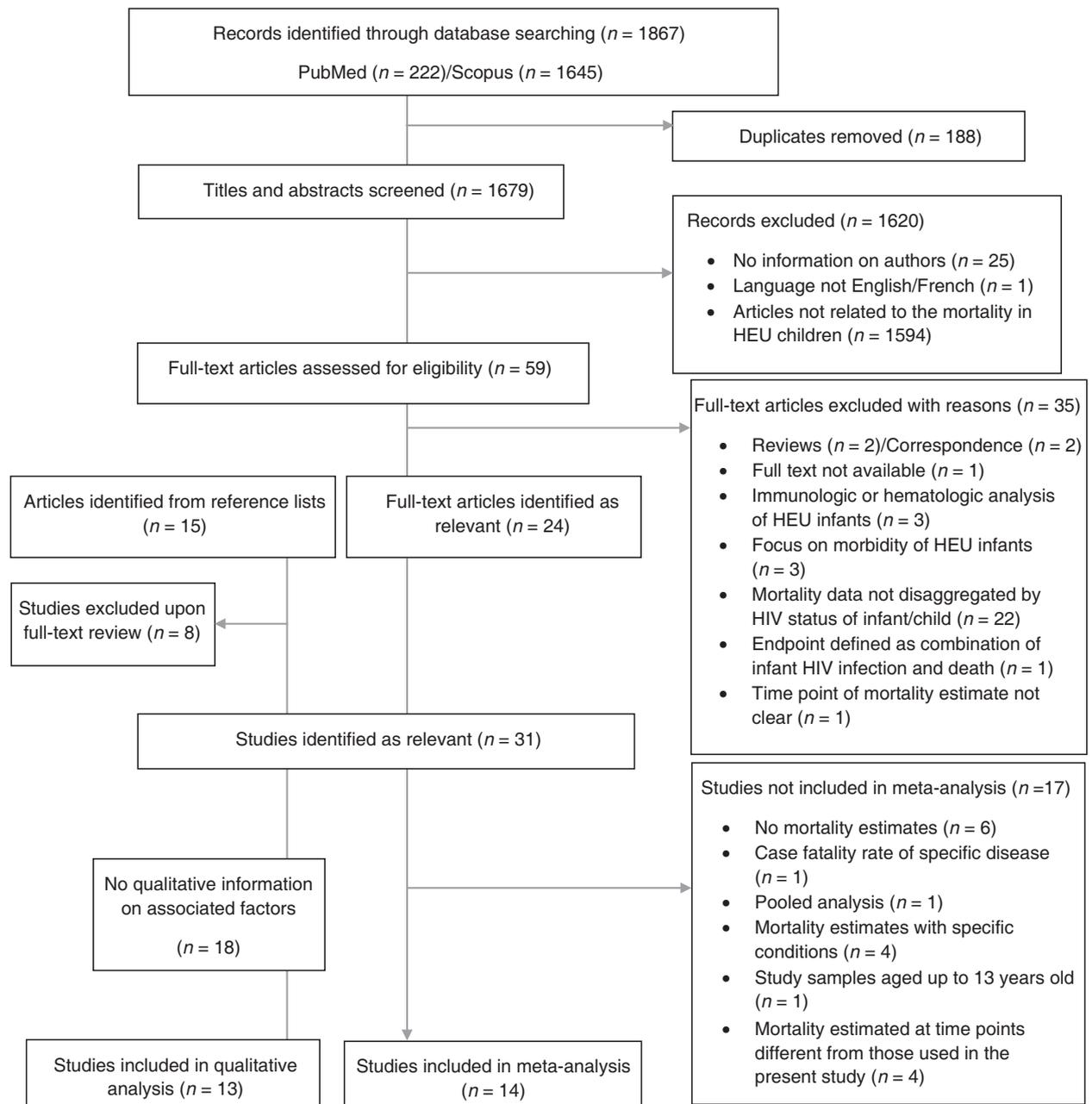
Records identified through database searching (*n* = 1867)

PubMed (*n* = 222)/Scopus (*n* = 1645)

Duplicates removed (*n* = 188)

Titles and abstracts screened (*n* = 1679)

Records excluded (*n* = 1620)

- No information on authors (*n* = 25)
- Language not English/French (*n* = 1)
- Articles not related to the mortality in HEU children (*n* = 1594)

Full-text articles assessed for eligibility (*n* = 59)

Full-text articles excluded with reasons (*n* = 35)

- Reviews (*n* = 2)/Correspondence (*n* = 2)
- Full text not available (*n* = 1)
- Immunologic or hematologic analysis of HEU infants (*n* = 3)
- Focus on morbidity of HEU infants (*n* = 3)
- Mortality data not disaggregated by HIV status of infant/child (*n* = 22)
- Endpoint defined as combination of infant HIV infection and death (*n* = 1)
- Time point of mortality estimate not clear (*n* = 1)

Articles identified from reference lists (*n* = 15)

Full-text articles identified as relevant (*n* = 24)

Studies excluded upon full-text review (*n* = 8)

Studies identified as relevant (*n* = 31)

Studies not included in meta-analysis (*n* =17)

- No mortality estimates (*n* = 6)
- Case fatality rate of specific disease (*n* = 1)
- Pooled analysis (*n* = 1)
- Mortality estimates with specific conditions (*n* = 4)
- Study samples aged up to 13 years old (*n* = 1)
- Mortality estimated at time points different from those used in the present study (*n* = 4)

No qualitative information on associated factors

(*n* = 18)

Studies included in qualitative analysis (*n* = 13)

Studies included in meta-analysis (*n* = 14)

Figure 1 Flow diagram of study selection.

were undertaken, except for Shapiro's study in Botswana where a small number of women had started maternal ART. Half the women in Bork's study also received 3 ARVs until cessation of breastfeeding at 6 months postpartum. It is noteworthy that the HEU infants in included studies had different exposures to breastfeeding both in terms of duration and modality due to changing recommendations on infant feeding by HIV-infected women over time. The estimated pooled 6-month cumulative mortality was 3.6% (95% CI: 2.6–4.7), based on the data on 8940 infants with 385 deaths (Figure 2b) with substantial heterogeneity ($I^2 = 84\%$). The study of

Table 1 Characteristics of the studies included in the meta-analysis

Author/Study	Country	Study enrolment year	Study design	No. of participants HEU	No. of participants HUU	Breastfeeding duration (month), median (IQR)	Breastfeeding pattern	Support for replacement feeding	Maternal ARVs/ART	Child cotrimoxazole
Becquet *et al.* 2007/Ditrame Plus [34]	Côte d'Ivoire	2001–2003	Secondary analysis of a prospective cohort study	507	0	4 (3–5)	50% short-term breastfed	Yes	No	N/A
Becquet *et al.* 2007/Ditrame [34]	Côte d'Ivoire, Burkina Faso	1995–1998	Secondary analysis of randomised controlled trial data	168	0	8 (6–10)	Predominantly long-term breastfeeding	N/A	No	N/A
Bork *et al.* 2014/ Kesho Bora [26]	Burkina Faso, Kenya, South Africa	2005–2008	Secondary analysis of randomised controlled trial data	751	0	N/A	Majority of women ever breastfed	N/A	One arm of mothers treated by ART from 28 to 36 weeks of pregnancy to 6.5 months post-partum	N/A
Brahmbhatt *et al.* 2006/Rakai [5]	Uganda	1994–1998	Secondary analysis of a prospective cohort study	269	3183	N/A	N/A	N/A	No	N/A
Chatterjee *et al.* 2007 [27]	Tanzania	1995–1997	Prospective cohort nested in clinical trial	682	0	N/A	N/A	N/A	No	N/A
Chilongozi *et al.* 2008/HIVNET 024 [28]	Malawi, Tanzania, Zambia	2001–2003	Observational cohort analysis of multisite trial data	1648	331	N/A	N/A	N/A	No	Yes
Kafulafula *et al.* 2010/NVAZ [29]	Malawi	2000–2003	Secondary analysis of randomised trial data	1810	0	N/A	Prolonged breastfeeding (>12 months)	N/A	No	N/A
Kafulafula *et al.* 2010/PEPI [29]	Malawi	2004–2007	Secondary analysis of randomised trial data	2035	0	N/A	Breastfeeding cessation by 6 months	Yes	No	Yes
Kourtis *et al.* 2013/BAN trial [30]	Malawi	2004–2010	Secondary analysis of randomised clinical trial data	2250	0	N/A	N/A	N/A	Maternal regimen group received triple ARVs until cessation of breastfeeding	Yes

Table I (*Continued*)

Author/Study	Country	Study enrolment year	Study design	No. of participants HEU	No. of participants HUU	Breastfeeding duration (month), median (IQR)	Breastfeeding pattern	Support for replacement feeding	Maternal ARVs/ART	Child cotrimoxazole
Kuhn et al. 2010/ZEBS trial [31]	Zambia	2001–2004	Secondary analysis of randomised trial data	749	0	N/A	All women breastfeeding with a half weaning at 4 months	Yes	No	Yes
Marinda et al. 2007/ZVITAMBO [4]	Zimbabwe	1997–2000	Secondary analysis of retrospective cohort study data	3135	9210	N/A	N/A	N/A	No	N/A
Rollins et al. 2013/Vertical Transmission Study [36]	South Africa	2001–2005	Intervention cohort study	943	1182	7 (6–9) for HEU and 9 (8–15) for HUU	All women breastfeeding; exclusive breastfeeding for the first 6 months encouraged	N/A	No	N/A
Shapiro et al. 2007/Mashi [6]	Botswana	2003	Prospective cohort study	534	137	6 for HEU and 9 for HUU (IQR: N/A)	All women breastfeeding; exclusive breastfeeding encouraged	Yes for HEU	ART became available from Oct 2002 to women with CD4 counts <200 or AIDS	No
Singh et al. 2011/SWEN [32]	India	2002–2007	Secondary analysis of trial data	644	0	N/A	N/A	N/A	Not available in public facilities Women who could afford to pay for ART received it (8%)	N/A
Venkatesh et al. 2011 [33]	South Africa	2000–2002	Secondary analysis of randomised controlled trial data	696	0	N/A	N/A	Yes	No	N/A
Wei et al. 2004 [35]	Tanzania	N/A	Prospective cohort	618	0	N/A	N/A	N/A	No	N/A

HEU, HIV-exposed uninfected (children); HUU, HIV-unexposed uninfected (children); IQR, Interquartile range; ARVs/ART, Antiretroviral drugs/antiretroviral treatment; N/A, Not available.

Table 2 Grade assessment

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of participants HEU	HUU	Relative risk (95% CI)	Quality
Quality assessment							No of participants			
Cumulative mortality at 3 months										
6	Observational studies	Not serious	Serious	Serious*	Not serious	N/A	131/5967 (2.2%)	N/A	Not estimable	Very low
Cumulative mortality at 6 months										
7	Observational studies	Serious†	Very serious‡	Serious*	Not serious	N/A	385/8940 (4.3%)	N/A	Not estimable	Very low
Cumulative mortality at 12 months										
11	Observational studies	Serious§	Very serious‡	Serious*	Not serious	N/A	891/14 507 (6.1%)	N/A	Not estimable	Very low
Cumulative mortality at 24 months										
4	Observational studies	Serious†	Very serious‡	Serious	Not serious	N/A	535/5100 (10.5%)	N/A	Not estimable	Very low
Relative mortality risk at 12 months										
4	Observational studies	Serious†	Very serious‡	Not serious	Serious¶	N/A	413/5995 (6.9%)	506/13 906 (3.6%)	RR 1.9 (0.9–3.8)	Very low
Relative mortality risk at 24 months										
3	Observational studies	Serious†	Very serious‡	Not serious	Serious¶	N/A	369/3938 (9.4%)	677/12 530 (5.4%)	RR 2.4 (1.1–5.1)	Very low

RR, relative risk.
*Studied population had different exposures to breast feeding, infant cotrimoxazole and maternal ARVs/ART.
†Risk of classification bias in Marinda's study.
‡High heterogeneity in between-study results.
§Risk of classification bias in Marida's and Wei's studies.
¶Small number of studies included.

Marinda *et al.* [4] seems to be the likely source of heterogeneity, pulling the overall estimate to a higher end. A possible explanation could be that 16% of infants classified as 'uninfected' in Marinda's study included those who had tested negative shortly after birth but who died subsequently without further testing. Thus, problems associated with misclassification of HIV-infected infants might explain the higher mortality rates. In a separate meta-analysis excluding Marinda's study, the pooled estimate was slightly attenuated to 3.4% (95% CI: 2.9–3.9) with significant reduction in heterogeneity ($I^2 = 11\%$) (data not shown).

Eleven studies contributed to the summary estimate of 12–month cumulative mortality (based on 14 507 HEU infants and 891 deaths observed by 12 months of age) [4,28–32,34–36]. The reported mortality rates varied considerably: the lowest estimate was 2.2% in India [32] and the highest was 10.5% in Tanzania [35]. Figure 2c shows the pooled mortality estimated at 5.5% (95% CI: 4.0–7.2) with extremely high heterogeneity ($I^2 = 94\%$). The high mortality rate reported by Wei *et al.* [35] in Tanzania should be understood in the context that the HEU and HIV-indeterminate infants were grouped for analysis, which might have caused overestimation of mortality rates. We attempted to address this classification bias by excluding the study of Wei *et al.* [35] and Marinda *et al.* [4] in a separate meta-analysis, which generated a pooled estimate of 4.8% (95% CI: 3.2–6.7), but still with high heterogeneity ($I^2 = 94\%$) (data not shown). Other potential sources of heterogeneity could be background infant mortality, duration of breastfeeding, exposure to infant cotrimoxazole, access to maternal ART (8% of women in Singh's study in India) [32], and use of short-term ART by one-third of women included in Kourtis's study in Malawi [30]. We were unable to account for these factors in subgroup analyses as the necessary information was not available.

Finally, we identified four studies reporting the cumulative mortality in HEU infants at 24 months of age [4, 6, 27,31]. Again, the reported mortality was subject to significant variability: 6.7% in a PMTCT trial in Botswana [6], 9.2% in Zimbabwe [4], 13.6% in Zambia [31] and 16.0% in Tanzania [27]. As shown in Figure 2d, the pooled cumulative mortality at 24 months was estimated at 11.0% (95% CI: 7.6–15.0). As in the case of previous estimates, heterogeneity among the study results was significantly high ($I^2 = 93\%$). This high heterogeneity remained ($I^2 = 93\%$) even after removing Marinda's study for the risk of bias with no significant modification in the mortality estimate (11.6%, 95% CI: 6.8–17.6) (data not shown).

Relative Risk of Mortality of HEU children compared to HUU children (Meta-analysis)

As stated earlier, there are few studies comparing mortality outcome between HEU and HUU children in the same setting. We identified four for the meta-analysis of the overall mortality risk ratio (RR) in these two groups at 12 months of age [4, 5, 28, 36]. A total of 5995 HEU and 13 906 HUU infants were included in the pooled analysis. These studies were undertaken in sub-Saharan Africa before ART was readily available for mothers. All the HEU infants in Chilongozi's study were given cotrimoxazole. Information on infant feeding modalities was available only in Rollins's study in which the majority of the infants received some type of breastfeeding with the median duration of 7 months for HEU and 9 months for HUU infants [36]. As shown in Figure 3a, the difference in pooled mortality of HEU and HUU infants at 12 months did not reach statistical significance (RR: 1.9, 95% CI: 0.9–3.8), possibly due to lack of statistical power and high underlying mortality for all children. The pooled estimate is again difficult to interpret in the presence of extremely high heterogeneity ($I^2 = 93\%$). The study by Marinda *et al.* [4] provides outlying results, and given the risk of classification bias in this study, we ran a separate analysis excluding it. The pooled RR estimate from the three remaining studies was 1.4 (95% CI: 1.0–1.8), indicating that HEU infants were likely to be at increased risk. There was no heterogeneity of study results ($I^2 = 14\%$) in this additional analysis (Figure 3b).

Figure 3c shows the result of the pooled analysis on comparative mortality risk at 24 months in HEU and HUU children. We included three cohort studies, comprising 3938 HEU and 12 530 HUU children [4–6]. In the study of Brahmbatt *et al.* [5] and Marinda *et al.*, [4] no mothers benefitted from maternal ART, whereas Shapiro's study included some women on ART. Also noteworthy was that all HEU children in Shapiro's study were breastfed for a median of 6 months while information on feeding modality was not available in the other two papers. The pooled estimate indicated that the mortality of HEU children was more than double that of HUU children at 24 months of age (RR: 2.4, 95% CI: 1.1–5.1). The level of heterogeneity was extremely high ($I^2 = 93\%$). As previously, we ran a separate analysis to address the risk of classification bias in Marinda's study. In this additional analysis, the difference between the groups did not reach statistical significance (RR: 2.0, 95% CI: 0.6–6.5) (Figure 3d). However, the removal of Marinda's study caused a substantial reduction of sample size, leading to a very large uncertainty interval. The residual heterogeneity still remained relatively high ($I^2 = 66\%$).

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(a)

Study	Rate (95% CI)	% Weight
Becquet 2007 (Ditrame Plus) (a)	0.03 (0.01, 0.04)	13.92
Becquet 2007 (Ditrame) (b)	0.02 (0.01, 0.05)	6.66
Kafulafula 2010 (PEPI) (c)	0.03 (0.02, 0.03)	23.43
Kafulafula 2010 (NVAZ) (d)	0.03 (0.02, 0.03)	22.79
Venkatesh 2011(e)	0.01 (0.00, 0.02)	16.31
Bork 2014 (f)	0.01 (0.01, 0.02)	16.88
Overall	0.02 (0.01, 0.03)	100.00

Q = 12.53, *P* = 0.03, I2 = 60%

(b)

Study	Rate (95% CI)	% Weight
Becquet 2007 (Ditrame Plus) (a)	0.03 (0.01, 0.04)	13.03
Becquet 2007 (Ditrame) (b)	0.02 (0.01, 0.05)	8.06
Marinda 2007	0.06 (0.05, 0.07)	17.54
Shapiro 2007 (c)	0.04 (0.02, 0.05)	13.24
Kafulafula 2010 (PEPI) (d)	0.03 (0.03, 0.04)	16.93
Kafulafula 2010 (NVAZ) (e)	0.04 (0.03, 0.05)	16.72
Bork 2014 (f)	0.02 (0.01, 0.04)	14.47
Overall	0.04 (0.03, 0.05)	100.00

Q = 36.68, *P* = 0.00, I2 = 84%

(c)

Study	Rate (95% CI)	% Weight
Wei 2004	0.11 (0.08, 0.13)	8.90
Marinda 2007	0.07 (0.07, 0.08)	9.76
Becquet 2007 (Ditrame Plus) (a)	0.03 (0.02, 0.05)	8.70
Becquet 2007 (Ditrame) (b)	0.03 (0.01, 0.06)	6.89
Chilongozi 2008 (c)	0.07 (0.06, 0.09)	9.56
Kafulafula 2010 (PEPI) (d)	0.08 (0.07, 0.09)	9.64
Kafulafula 2010 (NVAZ) (e)	0.07 (0.05, 0.08)	9.60
Kuhn 2010 (f)	0.09 (0.07, 0.12)	9.08
Singh 2011(g)	0.02 (0.01, 0.03)	8.94
Kourtis 2013 (h)	0.02 (0.02, 0.03)	9.67
Rollins 2013 (i)	0.04 (0.03, 0.05)	9.25
Overall	0.05 (0.04, 0.07)	100.00

Q = 175.35, *P* = 0.00, I2 = 94%

(d)

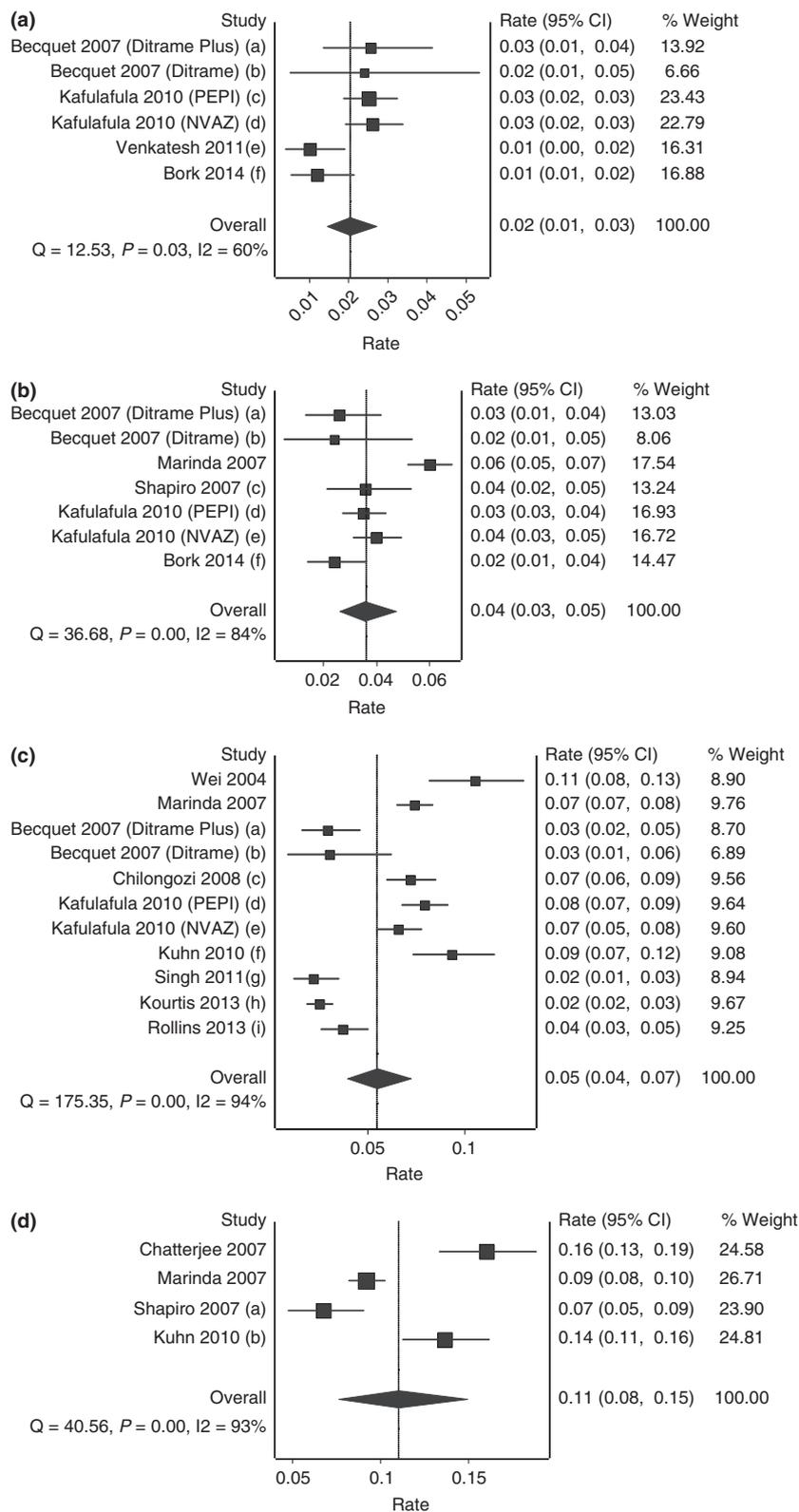| Study	Rate (95% CI)	% Weight
Chatterjee 2007	0.16 (0.13, 0.19)	24.58
Marinda 2007	0.09 (0.08, 0.10)	26.71
Shapiro 2007 (a)	0.07 (0.05, 0.09)	23.90
Kuhn 2010 (b)	0.14 (0.11, 0.16)	24.81
Overall	0.11 (0.08, 0.15)	100.00

Q = 40.56, *P* = 0.00, I2 = 93%

Figure 2 (a) Pooled 3-month cumulative mortality in HEU infants. *Note:* (a) 50% short-term breastfed group (median of 4 months), with support for replacement feeding. (b) Predominantly long-term breastfeeding (median of 8 months). (c) Breastfeeding cessation by 6 months, with support for replacement feeding. Infant cotrimoxazole. (d) Prolonged breastfeeding (>12 months). (e) Infants receiving ARV post-exposure prophylaxis. Mortality at 100 days. Subsidized formula. (f) Majority of women ever breastfed. ART arm receiving three ARVs from 28 to 36 weeks of pregnancy up to 6.5 months post-partum or breastfeeding cessation whichever first occurs. (b) Pooled 6-month cumulative mortality in HEU infants. *Note:* (a) 50% short-term breastfed group (median of 4 months), with support for replacement feeding. (b) Predominantly long-term breastfeeding (median of 8 months). (c) All infants were breastfed (median of 6 months). Maternal ART introduced during study. (d) Breastfeeding cessation by 6 months, with support for replacement feeding. Infant cotrimoxazole. (e) Prolonged breastfeeding (>12 months). (f) Majority of women ever breastfed. ART arm receiving three ARVs from 28–36 weeks of pregnancy up to 6.5 months post-partum or breastfeeding cessation whichever first occurs. (c) Pooled 12-month cumulative mortality in HEU infants. *Note:* (a) 50% short-term breastfed group (median of 4 months), with support for replacement feeding. (b) Predominantly long-term breastfeeding (median of 8 months). (c) Cotrimoxazole given to all infants. (d) Breastfeeding cessation by 6 months, with support for replacement feeding. Infant cotrimoxazole. (e) Prolonged breastfeeding (> 12 months). (f) All women breastfeeding with a half weaning at 4 months. Infants received weaning supplement and cotrimoxazole. (g) 8% of mothers with maternal ART. (h) Women randomized to receive triple ARVs until cessation of breastfeeding. Majority weaned at 6 months. Cotrimoxazole given to all infants. (i) Majority of infants received some type of breastfeeding (median of 7 months). (d) Pooled 24-month cumulative mortality in HEU children. *Note:* (a) All infants were breastfed (median of 6 months). Maternal ART introduced during study. (b) All women breastfeeding with a half weaning at 4 months. Children received cotrimoxazole.

Factors associated with increased mortality risk of HEU children

Given the diversity of definitions of variables and heterogeneity across studies, a narrative summary was considered appropriate. The following synthesis focused on direction of the association between different factors and the mortality outcome in HEU children. We identified 13 articles reporting the factors associated with the risk of mortality among HEU children.
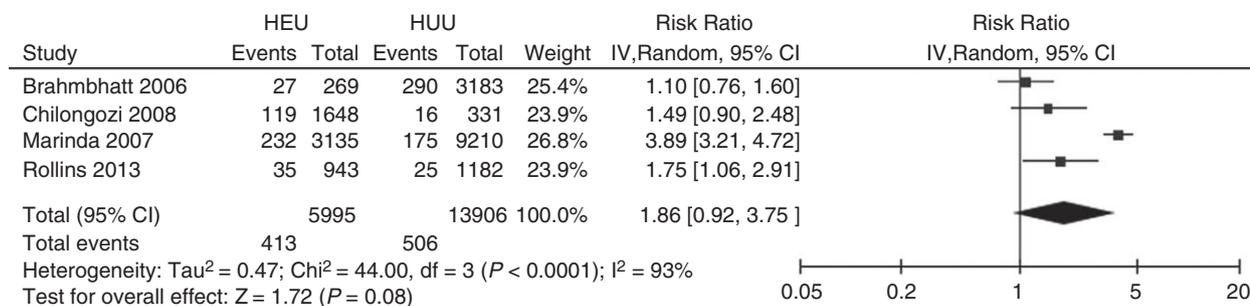
Maternal death and ill health

Maternal death significantly affects survival of uninfected children. However, the data are limited to the time when maternal ART was not available. In a large observational cohort in Zimbabwe, Marinda *et al.* [4] reported that HEU children whose mother had died were 2.7 times more likely to die (95% CI: 1.9–3.9) than those whose mothers survived. The pooled analysis of seven randomised trials in sub-Saharan Africa also identified a strong effect of mater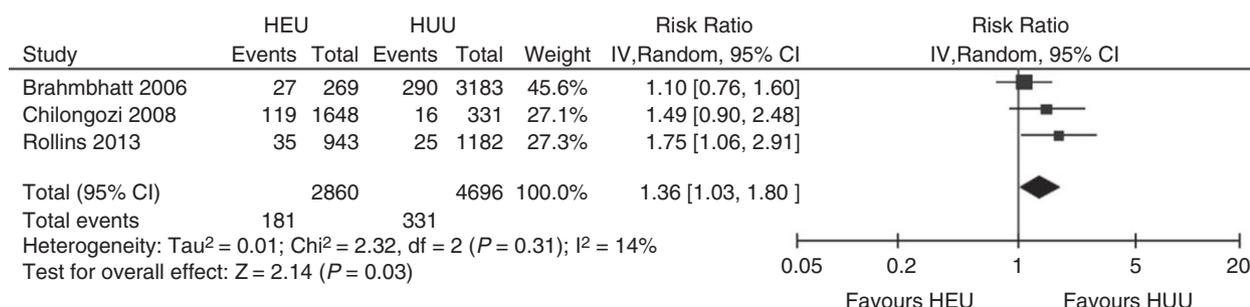nal death (adjusted odds ratio: 3.7, 95% CI: 1.9–7.0) on child mortality [15]. A significant association was also found in Zambia where hazard of death of HEU infants through 4 months of age was 16.2 times higher when the mother died within 4 months after delivery, after allowing for maternal CD4 counts, haemoglobin level and infant birthweight [23]. There is some evidence to suggest that the time of death of the mother impacts on the risk of death of her uninfected infant: Zaba *et al.* [38] reported that the mortality risk was tripled in the 2 years centring around the mother's death, irrespective of her HIV status.

The overall health status of mothers also plays a major role in the survival of uninfected infants. Reduced care or breastfeeding cessation as a result of maternal ill health or increased exposure to infectious pathogens in the households could explain increased risk of death of their uninfected infants [4, 9]. However, the definition of poor health and the indicators used varied between studies. Taha *et al.* [7] used maternal HIV clinical stage as an indicator to predict the risk of death in HEU infants and found a 1.8-fold increase in the hazard of death [adjusted hazard ratio (aHR): 1.8, 95% CI: 1.2–2.7] in children aged 6–15 months with mothers at advanced disease stage (3 or 4). A study in Tanzania also found an association of a borderline statistical significance (HR: 1.5, 95% CI: 1.0–2.3) between the mortality through 24 months and advanced maternal HIV stage (defined as WHO disease stage 2 or higher) [27]. In this study, higher maternal viral load at delivery (≥50 000 copies/ml) was associated with a sevenfold (95% CI: 2.4–23.7) increase of mortality hazard through 24 months of age in HEU children. Several studies have shown the association between low maternal haemoglobin level and increased child mortality risk: Kuhn *et al.* [23] reported that a maternal haemoglobin level <10 g/dl was significantly associated with HEU infant mortality through 4 months of age (aHR: 2.4, 95% CI: 1.1–5.4). Marinda *et al.* [4] also found that HEU infants with mothers with haemoglobin <70 g/dl were at 3.8 times higher risk of dying than those of mothers with haemoglobin above the threshold (95% CI: 2.1–7.0). Such an association was however not found in HEU children aged up to 24 months in Tanzania when the risk of death was compared between those with maternal haemoglobin below and above 8.5 g/dl [27].
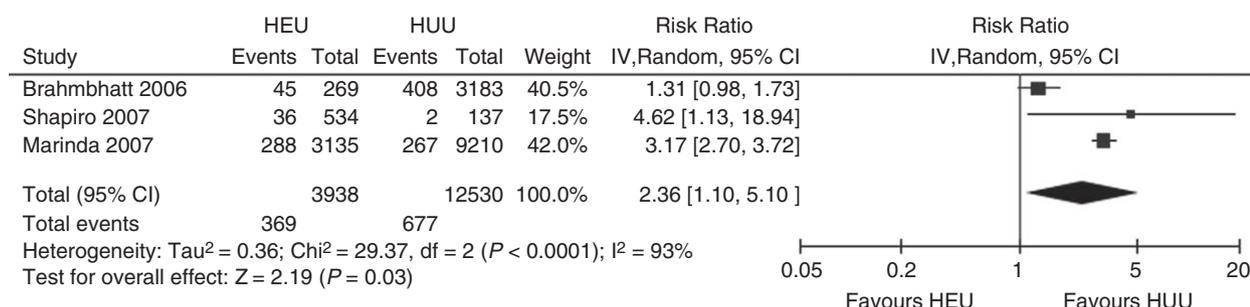
S. Arikawa *et al.* **Mortality in HEU children**

(a) Mortality risk ratio at 12 months between HEU and HUU infants

	HEU		HUU			Risk Ratio	Risk Ratio
Study	Events	Total	Events	Total	Weight	IV,Random, 95% CI	IV,Random, 95% CI
Brahmbhatt 2006	27	269	290	3183	25.4%	1.10 [0.76, 1.60]	
Chilongozi 2008	119	1648	16	331	23.9%	1.49 [0.90, 2.48]	
Marinda 2007	232	3135	175	9210	26.8%	3.89 [3.21, 4.72]	
Rollins 2013	35	943	25	1182	23.9%	1.75 [1.06, 2.91]	
Total (95% CI)		5995		13906	100.0%	1.86 [0.92, 3.75]	
Total events	413		506				

Heterogeneity: Tau² = 0.47; Chi² = 44.00, df = 3 (*P* < 0.0001); I² = 93%
Test for overall effect: Z = 1.72 (*P* = 0.08)

(b) Mortality risk ratio at 12 months between HEU and HUU infants (excluding Marinda 2007)

	HEU		HUU			Risk Ratio	Risk Ratio
Study	Events	Total	Events	Total	Weight	IV,Random, 95% CI	IV,Random, 95% CI
Brahmbhatt 2006	27	269	290	3183	45.6%	1.10 [0.76, 1.60]	
Chilongozi 2008	119	1648	16	331	27.1%	1.49 [0.90, 2.48]	
Rollins 2013	35	943	25	1182	27.3%	1.75 [1.06, 2.91]	
Total (95% CI)		2860		4696	100.0%	1.36 [1.03, 1.80]	
Total events	181		331				

Heterogeneity: Tau² = 0.01; Chi² = 2.32, df = 2 (*P* = 0.31); I² = 14%
Test for overall effect: Z = 2.14 (*P* = 0.03)

(c) Mortality risk ratio at 24 months between HEU and HUU children

	HEU		HUU			Risk Ratio	Risk Ratio
Study	Events	Total	Events	Total	Weight	IV,Random, 95% CI	IV,Random, 95% CI
Brahmbhatt 2006	45	269	408	3183	40.5%	1.31 [0.98, 1.73]	
Shapiro 2007	36	534	2	137	17.5%	4.62 [1.13, 18.94]	
Marinda 2007	288	3135	267	9210	42.0%	3.17 [2.70, 3.72]	
Total (95% CI)		3938		12530	100.0%	2.36 [1.10, 5.10]	
Total events	369		677				

Heterogeneity: Tau² = 0.36; Chi² = 29.37, df = 2 (*P* < 0.0001); I² = 93%
Test for overall effect: Z = 2.19 (*P* = 0.03)

(d) Mortality risk ratio at 24 months between HEU and HUU children (excluding Marinda 2007)

	HEU		HUU			Risk Ratio	Risk Ratio
Study	Events	Total	Events	Total	Weight	IV,Random, 95% CI	IV,Random, 95% CI
Brahmbhatt 2006	45	269	408	3183	65.6%	1.31 [0.98, 1.73]	
Shapiro 2007	36	534	2	137	34.4%	4.62 [1.13, 18.94]	
Total (95% CI)		803		3320	100.0%	2.02 [0.62, 6.54]	
Total events	81		410				

Heterogeneity: Tau² = 0.53; Chi² = 2.96, df = 1 (*P* = 0.09); I² = 66%
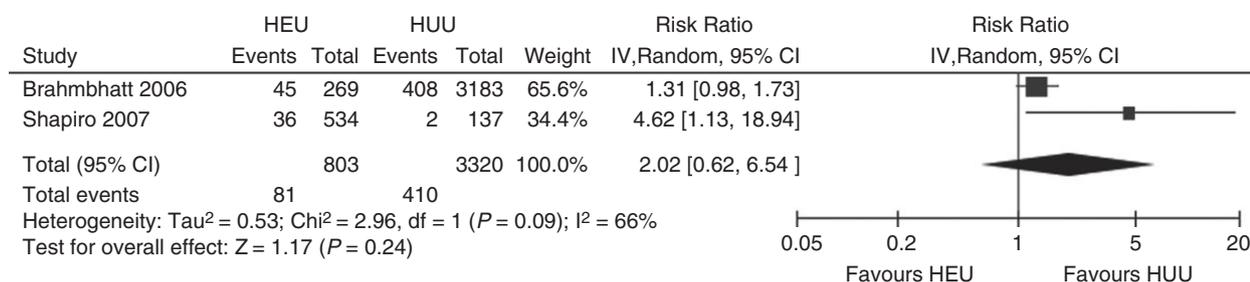Test for overall effect: Z = 1.17 (*P* = 0.24)

Figure 3 (a) Mortality risk ratio at 12 months between HEU and HUU infants. (b) Mortality risk ratio at 12 months between HEU and HUU infants (excluding Marinda [4]). (c) Mortality risk ratio at 24 months between HEU and HUU children. (d) Mortality risk ratio at 24 months between HEU and HUU children (excluding Marinda [4]).

Studies have shown mixed results with regard to the impacts of maternal CD4 counts. Kuhn *et al.* [23] found in Zambia that HEU infants born to mothers with CD4 cell counts <350 cells/μl were significantly more likely to die during the first 4 months, after adjusting for maternal death and low birthweight (HR: 2.9 with 95% CI: 1.0–8.0). Further analysis on the same population confirmed this association through 18 months of life: the mortality hazard in children with mothers having low CD counts (<200 cells/μl) was 3.2 times higher (95% CI: 1.3–8.1) than in those with higher maternal CD4 counts (>500 cells/μl) [39]. Similar results were put forward by a study in Zimbabwe: HEU children born to mothers with CD4 count <200/μl were at 2.6 higher risk of dying than those born to mothers with CD4 counts ≥400/μl (95% CI: 1.8–3.8), allowing for infant's birthweight, sex, mother's marital status and household income [4]. A pooled analysis of seven randomised trials in sub-Saharan Africa showed that risk of death among HEU infants was 1.7 times higher when maternal CD4 counts were <200/μl compared to when they were above 500/μl, although the result did not reach statistical significance [15]. Similarly, no significant effects of maternal CD4 counts during pregnancy on the mortality of HEU infants through 48 weeks were observed in the Antiretrovirals and Nutrition (BAN) clinical trial in Malawi [30].

Infant feeding practices

Our literature review revealed complexity of the issues related to infant feeding, with inconsistent results between studies suggesting that findings may be context-specific. Some studies showed that type and duration of infant feeding was associated with the risk of death among HEU infants. Data from the Kesho Bora trial showed that never breastfed infants or early weaned infants were seven times more likely to die within 6 months after birth than infants still being breastfed, after controlling for confounders including infant's HIV infections status (95% CI: 2.5–17.9) [8]. Similar findings were put forward in a study in Malawi: analysing cumulative mortality at 6–15 months of age, Taha *et al.* [7] found that the mortality rate at 15 months was nearly double in never breastfed or early weaned HEU infants as that of infants breastfed for long durations (*P* = 0.04). The study has suggested long-term adverse impacts of early weaning given that this difference became significant only after 12 months of age [7]. Kourtis *et al.* [30] further highlighted that the mortality of HEU infants increased after 28 weeks of age, the timing of which corresponds with weaning from breastmilk for the majority of infants in the cohort.

However, a comparative study of two trials in Uganda showed that overall all-cause infant mortality did not statistically significantly differ between the trial in which HEU children were weaned earlier (median 4 months) and the trial with later weaning (median 9 months) [24]. In urban South Africa, infant feeding modality was not associated with increased risk of mortality at 3 months of age among HEU infants; mothers in this study had fairly good access to safe replacement feeding including clean water and infant formula [33]. An absence of significant associations between infant feeding modality and mortality risk was also reported by the pooled analysis of seven PMTCT trials in sub-Saharan Africa [15]. Early cessation of breastfeeding (i.e. before 4 months) was not significantly associated with the hazard of death among HEU infants in an observational cohort in Malawi after adjusting for other covariates including maternal CD4 counts and vital status [23].

Low birthweight

Data from a randomised trial in Tanzania showed that low birthweight was significantly associated with neonatal and post-neonatal mortality among HEU infants [35], which confirms the findings of the multisite pooled analysis in sub-Saharan Africa [15] and those of an observational cohort in Zambia [23]. Retrospective analysis of a cohort study in Kenya further revealed that low birthweight was associated with a 3.3-fold increased hazard of dying among HEU infants after adjusting for maternal viral load (95% CI: 1.1–10.0) [40]. However, it may be difficult to distinguish low birthweight from preterm appropriate for gestational age and to assess its effects from other factors including breastfeeding.

Discussion

HEU infants and children are at increased risk of mortality, although the differences between HEU and HUU were statistically significant only for the estimate at 24 months. Our pooled estimates on cumulative mortality of HEU at 3, 6, 12 and 24 months of age were 2.0%, 3.6%, 5.5% to 11.0%, respectively. Our estimates are comparable with previous results of a pooled analysis of seven PMTCT trials in sub-Saharan Africa in the pre-ART era in which the mortality estimates in HEU children were 4.9% at 12 months and 7.6% at 24 months [15]. Compared to the WHO estimates of infant mortality in the sub-Saharan region in 2013 (61/1000 live births) [35], our estimate at 12 months is similar, suggesting that HEU infants may not be at increased risk compared to the general population. Compared to HUU,

estimated relative mortality in HEU children at 12 months of age is nearly double, although the difference does not reach statistical significance; at 24 months of age, there is a statistically significant doubling in risk between the two groups but statistical significance is lost once the study with bias concerns is removed [4]. All four studies contributing to the pooled estimate of relative risk at 12 months were from the pre-ART era [4, 5, 28, 36]. For 24 months of age, only one [6] of three studies [4, 5] had data on mothers on ART.

The strength of our review lies in the systematic identification and analysis of studies, with no restrictions on study design and geographical locations; this enabled us to analyse 14 articles, mostly from the pre-ART era, with mortality data on HEU infants and 13 articles reporting on associated factors. The quality and potential bias of included studies were adequately addressed, which gave important consideration to the interpretation of pooled estimates.

The major limitation is the heterogeneity of study results. The pooled estimates are useful as they provide a summary of what is published so far on the mortality risk of HEU infants at different ages. Nevertheless, our results must be interpreted with caution due to substantial heterogeneity, with the value of I^2 statistics ranging from 60% to 95%. Our effort to remove the studies with outlying results made little difference and residual heterogeneity persisted. Factors that may explain such high heterogeneity include inconsistency in the coverage of maternal ART and PMTCT prophylaxis in the studied populations. While our meta-analyses used data mostly from studies conducted before the widespread use of ART, two studies included some women already benefiting from ART [6, 32] and another two included women randomised to receive ART until cessation of breastfeeding at 6 months post-partum [26, 30]. As highlighted in our qualitative review, maternal survival and health significantly improve survival probability of their uninfected infants. The association between mortality and duration of breastfeeding is also reported by the reviewed literature. Maternal ART, whether for mother's own health or to ensure appropriate nutritional or immunological benefits for infants through breastfeeding, is very likely to impact on the mortality of HEU infants. Two studies demonstrate either a direct association between ART and improved under-5 mortality of all infants [42] or the importance of ART availability with ecological association between maternal survival and reduced mortality of infants younger than 2 years [43]. Due to lack of information, we were unable to assess the contribution of maternal exposure to ART to overall heterogeneity in the pooled estimates. The evidence regarding maternal survival and infant feeding in relation to the mortality of

HEU children needs to be substantiated in the post-ART era. Another possible source of heterogeneity is children's different exposure to cotrimoxazole prophylaxis, which may have survival benefits [4, 25, 30]. The mortality risks in the study of Chilongozi might have been underestimated as the children were routinely given cotrimoxazole. Children in three other studies [29–31] also were given cotrimoxazole, but details of coverage were unknown, excluding subgroup analyses by cotrimoxazole exposure. Finally, heterogeneity related to context-specific factors, such as background mortality and access to health care, may have been important.

Conclusion

As the use of maternal ART expands, the number of HEU infants continues to increase globally. We need a better understanding of the risks faced by this vulnerable group. Our results suggest that early mortality of HEU infants might not be significantly different from that of general population or HUU infants living in the same community but may become significant when considering the overall period to 2 years of age. However, heterogeneity between studies and lack of high-quality data comparing the mortality of HEU and HUU infants limits interpretation of the pooled estimates. More data from the post-ART era are needed to understand the impact of maternal health on breastfeeding and on the survival of HEU infants. Further research is needed to inform more precise estimates of HEU infant mortality and to identify strategic interventions to reduce mortality risks in this vulnerable population.

Disclaimer

The findings of the analyses and content of the manuscript are the views of the authors and do not reflect the position of WHO or other institutions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.
Appendix S2. Articles included in the meta-analysis (*n* = 14) and those excluded with reasons (*n* = 11).

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