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HIV-exposed Uninfected Infant Morbidity and Mortality within a Nationally Representative Prospective Cohort of Mother-Infant Pairs in Zimbabwe, 2013–2014

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Abstract

Objective: To examine morbidity and mortality risk among HIV-exposed uninfected (HEU) infants.

Design: Secondary data analysis of HEU infants in a prospective cohort study of mother-infant pairs.

Methods: Infants were recruited from immunization clinics (n=151) in Zimbabwe from February-August 2013, enrolled at 4–12 weeks age, and followed every 3 months until incident HIV-infection, death, or 18 months follow-up. We estimated cumulative mortality probability and hazard ratios (HR) with 95% confidence intervals (CI) using Kaplan-Meier curves and Cox regression, respectively. We also described reported reasons for infant hospitalization and symptoms preceding death. Median weight-for-age z-scores (WAZ) and median age were calculated and analyzed across study visits.

Results: Of 1188 HIV-exposed infants, 73 (6.1%) contracted HIV; we analyzed the remaining 1115 HEU infants. In total, 54 (4.8%) infants died, with median time to death of 5.5 months since birth (IQR:3.6–9.8 months). Diarrhea, difficulty breathing, not eating, fever, and cough were commonly reported (range: 7.4%−22.2%) as symptoms preceding infant death. Low birth weight was associated with higher mortality (adj-HR 2.66, CI:1.35–5.25), while maternal ART pre-delivery (adj-HR 0.34, CI 0.18–0.64) and exclusive breastfeeding (adj-HR 0.50, CI:0.28–0.91) were associated with lower mortality. Overall, 9.6% of infants were hospitalized. Infant median WAZ declined after 3 months of age, reaching a minimum at 14.5 months of age, at which 50% of infants were underweight (WAZ below −2.0).

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Conclusions: Clinical interventions including maternal ART; breastfeeding and infant feeding counseling and support; and early prevention, identification, and management of childhood illness; are needed to reduce HEU infant morbidity and mortality.

Keywords

HIV-exposed uninfected infants; morbidity; mortality; Zimbabwe

INTRODUCTION

The aim of prevention of mother-to-child transmission (PMTCT) programs is HIV-free survival among HIV-exposed infants. Substantial global progress has been made in PMTCT in recent years, including in Zimbabwe, where the number of new HIV infections annually among children was reduced by 64% from 12,000 in 2010 to 4,300 in 2017.[1] In Zimbabwe, adoption of policies such as Option B+ in 2013 recommending lifelong antiretroviral therapy (ART) for pregnant and breastfeeding women and Treat All in 2015 recommending ART for all people living with HIV regardless of clinical or immunological criteria, have facilitated timely ART access among women of reproductive age.[2, 3] As a result, there is a growing number of HIV-exposed infants who are uninfected and WHO estimates that HIV infection has been averted in approximately 79,500 infants in Zimbabwe from 2010 to 2017.[1]

Despite this achievement, keeping HIV-exposed uninfected (HEU) infants healthy and alive remains a challenge, particularly in resource-limited settings like Zimbabwe where infant mortality is 36 deaths per 1000 live births and the most frequent non-AIDS related causes of death are estimated to be due to diarrhea (9.8%) and pneumonia (12.8%).[4] There is substantial evidence that HEU infants have a high risk of morbidity and mortality, particularly compared to infants who are HIV-unexposed.[5–8] Many of the contributing studies were however conducted prior to widespread access to ART and/or in clinical trial settings with relatively few infants. As a result, their findings may not be as generalizable to current HEU infants receiving clinical services in routine settings. We examined risk of morbidity and mortality among HEU infants receiving routine clinical services at public health facilities in Zimbabwe.

METHODS

We analyzed data on HEU infants identified in a prospective observational cohort study of MTCT transmission in Zimbabwe. Methods of this parent study have been fully described elsewhere.[9] Briefly, this study included a nationally representative sample of mother and HIV-exposed infant pairs in Zimbabwe recruited from immunization clinics (n=151) from February-August 2013. Infants were enrolled at 4–12 weeks age and followed and tested for HIV DNA polymerase chain reaction (PCR) testing via dried blood spot (DBS) roughly every 3 months until incident HIV-infection, death, or 18 months follow-up. This resulted in a maximum of 7 study visits including baseline and follow-up, which were integrated with routine clinical care and included a questionnaire administered to the mother or caregiver and abstraction of selected clinical variables from the child's Child Health Card (CHC). We defined an infant as HEU if he or she was: 1. born to a mother with HIV-status confirmed

based on data from the child health card, antenatal care card, and maternal outpatient card, and 2. not diagnosed with HIV during the period of follow-up.

Infant characteristics collected at baseline included age, gender, infant postnatal visits, exposure to TB in the household, birth weight (low defined as <2.5 kg), delivery location (hospital or not), mode of transport to health facility (motorized or walking), feeding practices 0 to 4–12 weeks (exclusive breastfeeding or not), and infant hospitalization. Maternal characteristics collected at baseline included age, marital status (married/cohabitating or not), education (highest level completed), socio-economic status by quintiles, maternal postnatal visits beyond the baseline visit, timing of maternal ART initiation (did not initiate ART prior to 12 weeks post-delivery, initiated ART pre-conception, initiated ART during conception, initiated ART during pregnancy, initiated ART post-delivery, but prior to 12 weeks), CD4 count (> 350 or ≤350 cells/mm^3), gestational age at first ANC visit, maternal hospitalization after giving birth prior to 12 weeks post-delivery, and maternal prenatal visit attendance.

Our primary outcome of interest was all-cause infant mortality. We estimated cumulative mortality probability and hazard ratios (HR) with 95% confidence intervals (CI) for HEU using Kaplan-Meier curves and Cox regression, respectively. Infants who were lost to follow-up (LTFU) or suspended from the study for other reasons (refusal to continue or relocation) were censored from mortality analyses on the date recorded on the study suspension form or the date recorded at the last study visit. Differences in cumulative survival curves were compared using the log-rank test.

We described and assessed for differences in percentage and median values for categorical and continuous maternal and infant characteristics by infant mortality among HEU infants using a two-sided log-rank test. Crude, full, and reduced regression models were used to generate final HR estimates for selected baseline characteristics that significantly differed by HEU infant mortality. Full models were adjusted for all other baseline characteristics as potential confounders unless they were missing for a substantial proportion of observations (>10%). Reduced models for each covariate were adjusted only for factors resulting in ≥5% change in the fully adjusted estimate using a backwards elimination method, per purposeful selection of covariates as described by Hosmer and Lemeshow.[10, 11] This analysis included all infants who did not experience the primary endpoint of the parent study (HIV infection via mother-to-child transmission) so the analyses were not weighted for the complex survey design of the parent study.

Our secondary outcomes of interest were infant hospitalization, infant postnatal visits after the baseline visit, symptoms preceding infant death, and sub-standard infant growth, as indicators of infant morbidity and health-seeing behavior. We described the frequency of reported infant hospitalization, reasons for infant hospitalization (which were non-mutually exclusive, meaning that the mother/caregiver could have reported more than one reason), and symptoms preceding death among HEU infants who died during follow-up. We also described the frequency of postnatal infant and maternal visits beyond the baseline visit, including median time to visit. Weight-for-age z-scores (WAZ) were calculated for the subset of infants who had current weight recorded on their CHC and abstracted by staff at

each study visit using the most recently available World Health Organization Child Growth Standards for children 0–2 years of age.[12] Median WAZ and median age in months was calculated among infants at each study sequential study visit (1 through 7). Data was included for all infants, even if they did not contribute data at all 7 study visits due to censoring from the study or missing weight data on the CHC; this approach was selected after a sensitivity analysis restricted to only infants who had data at all 7 study visits (n=371 infants) produced similar results.

All statistical analyses were conducted in SAS 9.4 (Cary, NC) and an alpha of 0.05 was used for tests of statistical significance. The study protocol for the parent study was approved by the Zimbabwe Medical Research Council. The study protocol was also reviewed in accordance with the US Centers for Disease Control and Prevention (CDC) human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes.

RESULTS

Of 1188 HIV-exposed infants in the study, 73 (6.1%) contracted HIV; the remaining 1115 HEU infants were included in our analysis. The median age of infants at last follow-up was 15.6 months (IQR: 13.6–16.3) and retention through the end of study follow-up was 73.5%.

Table 1 shows the distribution of baseline characteristics among HEU infants and their mothers overall, and by mortality status at the end of follow-up. The median age of HEU infants at baseline was 6.6 weeks (6.0–8.9 weeks) and half (51.4%) were male. The majority (85.8%) of HEU infants were born in a health facility and means of transport to bring them to the clinic was by walking (73.8%). From birth to 4–12 weeks, nearly all HEU infants were breastfed and 70.3% were exclusively breastfed; the median duration of breastfeeding was 14.2 months (IQR: 7.8–16.8 months). Mothers of HEU infants had a median age of 29 years (24–33 years). Most (87.6%) were married or cohabitating with a partner and had completed an 8^{th} grade or higher education level (64.3%). Median gestational age first ANC visit was 20 weeks (IQR: 16–26 weeks); however, gestational age was missing on 19.4% of all women. Few (1.7%) of mothers were hospitalized after birth to 12 weeks post-delivery. Nearly half (47.1%) of mothers of HEU infants had a baseline CD4 ≤350 cells/mm^3 ; however, baseline CD4 was missing on a quarter of women. Most (65.7%) women initiated ART pre-delivery (36.4% pre-conception and 29.3% during pregnancy) and few women initiated ART post-delivery but prior to 12 weeks (9.6%); 24.7% of women did not initiate ART post delivery prior to 12 weeks. One-fifth (21.4%) of infants were exposed to TB through their mothers or other household contacts. Diphtheria, pertussis, tetanus vaccine first dose (DPT1) coverage based on the available immunization card held by the mother/guardian was 84.3% at baseline; however, 11.9% of HEU infants had incomplete immunization information during follow-up, precluding further analysis of immunization status.

Figure 1 shows the median and IQR of WAZ scores for HEU infants with weight data available during follow-up. Median infant growth was slightly above or at the normal z-score

value of 0 from birth to 3 months; then steadily declined to reach a minimum of −2.0, the WHO cut-off value for underweight; and then rebounded from 14.5 months to 17.6 months to reach a median value of −1.2. Stratified curves by low birth weight, exclusive breastfeeding, and maternal age showed a similar trajectory (not shown). Nearly all infants had WAZ score available at baseline (n=1113, 99.8%); however, the percent of infants with weight available decreased and varied over later time points and ranged from 50.5% to 71.1%. Missing WAZ score at the post-baseline visit was more common among infants without any routine postnatal visit beyond the baseline visit (60.3% vs. 5.1%) or without any hospitalization visit (50.6% vs. 39.3%) but did not differ on other demographic or clinical factors.

In total, 54 (4.8%) HEU infants died during follow-up with a median time to death of 5.5 months since birth (IQR: 3.6–9.8 months). The most common symptoms reported preceding death were diarrhea (n=12, 22.2%), difficulty breathing (n=8, 14.8%), not eating (n=9, 16.7%), fever (n=5, 9.3%), and cough (n=4, 7.4%). A total of 84 (7.5%) HEU infants had mothers who died either prior to or after enrollment; of these, one infant died during follow-up. The percentage of HEU infants with low birth weight was 11.1% and was higher among those HEU who died during follow-up than those HEU infants who remained alive during follow-up (22.9% v. 10.6%, p=0.009). Mixed feeding (versus exclusive breastfeeding) during the first 4–12 weeks of life was more frequent among those HEU who died compared to those who remained alive during follow-up (44.2% v. 26.6%, p=0.020), with very few HEU infants overall who received no breastfeeding (n=25, 2.3%). No ART pre- or post-delivery, but within 12 weeks (i.e. at all during follow-up) among mothers was more frequent among HEU infants who died compared to those who remained alive during follow-up (44.4% v. 23.7%, p<0.0001).

Postnatal visits after the baseline visit were uncommon in this cohort overall with 17.7% having any postnatal infant visit and 14.4% having any postnatal maternal visit. Median time to first postnatal visit after baseline visit was 12 weeks (IQR: 8–14) for maternal visits and 12 weeks (IQR: 10–14) for infant visits.

During follow-up, 9.6% (n=107) of infants and 6.6% (n=74) of mothers were hospitalized at least once, with a median of 1 visit (IQR: 1–2) for both. Of the 107 hospitalized infants, reported reasons for hospitalization were rash (5.6%), diarrhea (28.0%), coughing (39.3%), and fever (50.5%).

Due to non-significant difference (p=0.75), we combined ART pre-conception and during pregnancy, as “ART pre-delivery” in mortality analyses. Mortality during follow-up was 8.7% among HEU infants whose mothers never initiated ART, 3.6% among those whose mothers initiated ART pre-delivery, and 2.8% among those whose mothers initiated ART post-delivery, but prior to 12 weeks. Figure 2 shows cumulative mortality over time was significantly higher among infants whose mothers were not on ART compared to those whose mothers were on ART pre-delivery or on started on ART post-delivery, but prior to 12 weeks. Mortality was slightly higher among those HEU infants whose mothers initiated ART pre-delivery compared to those who initiated ART post-delivery, but prior to 12 weeks; however this difference was not statistically significant. As shown in Table 2, maternal ART

pre-delivery was associated with significantly lower risk of mortality among HEU compared to no maternal ART (adj-HR 0.26, 95% CI: 0.14–0.47), independent of infant feeding practices, low birth weight, and maternal age. Maternal ART post-delivery, but prior to 12 weeks versus. no maternal ART had a similar association (adj-HR 0.22, 95% CI: 0.07–0.74).

Mortality during follow-up was 9.4% (11/117) among HEU infants who were low birth weight (<2.5 kg) and 4.0% (37/934) among HEU infants who were not low birth weight. Figure 3 shows cumulative mortality over time was significantly higher among HEU infants who were low birth weight compared to those who were not low birth weight. As shown in Table 2, low birth weight was associated with significantly higher mortality among HEU infants (adj-HR 2.66, 95% CI: 1.35–5.25), independent of maternal ART timing and maternal age.

Mortality during follow-up was 3.6% (28/772) among HEU infants who were exclusively breastfed and 7.4% (24/326) among those who were not exclusively breastfed (mixed fed or not breastfed). Figure 4 shows a cumulative mortality over time was significantly lower among HEU infants who were exclusively breast fed compared to those who were not exclusively breastfed. As shown in Table 2, exclusive breastfeeding was associated with significantly lower mortality among HEU infants (adj-HR 0.50, 95% CI: 0.28–0.91), independent of low birth weight, infant postnatal visits, and maternal age.

DISCUSSION

Overall the mortality we observed in our cohort (4.8%) is similar to that reported in a pooled analysis of data on 19,219 HEU infants across 21 clinical trials conducted from 1995 to 2015 in sub-Saharan Africa, estimated as 4.5% at 12-months and 5.5% at 2 years.[7] Mortality in our analysis is also lower than 2-year mortality of 9.2% observed among HEU infants Zimbabwe in the ZVITAMBO study.[13] This difference is not surprising, as the ZVITAMBO study was conducted in a timeframe where ART access was limited. The calculated mortality rate based on 54 observed deaths among 1115 live births in cohort of HEU infants in Zimbabwe would be 48 deaths per 1000 live births; was is higher than overall infant mortality rate in Zimbabwe (36 deaths per 1000 live births). The reason for this higher mortality among HIV-exposed uninfected infants has been explored in other studies, is likely multifactorial and not explicitly known, but may be related to socio-economic risk factors of living in HIV-affected households, immune activation and systematic inflammation stemming from in-utero and postnatal HIV exposure, and prolonged exposure to ART during the developmentally sensitive period from conception through breastfeeding.[5]

Significant predictors of HEU infant mortality identified in our study are consistent with those from the aforementioned pooled analysis, where maternal ART (adj-HR 0.51, 95% CI: 0.28–0.94) was protective, while low birth weight (adj-HR 2.92, 95% CI: 2.51–3.39) and never breastfeeding (adj-HR 2.48, 95% CI: 1.95–3.16) were associated with increased mortality.[7] In addition, the pooled analysis also found maternal CD4<350 (adj-HR 1.43, 95% CI: 1.24–1.66) and maternal death (adj-HR 11.08, 95% CI: 8.25–14.89) as predictive

of HEU infant mortality; we were not able to assess these in our analysis due to limited available data.

Our finding of poor growth among HEU infants is consistent with findings from three other studies in sub-Saharan Africa. The ZVITAMBO study also found a steadily declining poor growth trajectory in HEU infants with mean length-for-age (LAZ) z-score ranging from −1.02 at 6 weeks to a minimum value of −1.49 at 18 months.[14] A study of HIV-exposed infants in Tanzania in the ART-era, showed a declining trajectory of WAZ among HEU infants over time from 6 weeks of age, and reached a minimum across infants at 60 weeks of age (13.8 months), which is similar to our finding of a minimum median z-score at 14.5 months.[15] The overall WAZ curve was lower and showed a steeper decline in our cohort (minimum median z-score of −2.0 v. approximately −0.75), however, this may reflect the clinical trial setting of the Tanzania study in which children received frequent growth monitoring and micronutrient supplementation beyond standard of care.[15] A similar study of HIV-exposed infants in Kenya, found a similar trajectory of LAZ with a similar decline and magnitude of z-scores after birth with a minimum of −1.5 at about 15 months of age; however, this study also included infants with HIV infection and was done in 2000, pre-ART.[16]

The most common causes of death among HEU infants in the ZVITAMBO study were acute respiratory illness (57.7%), malnutrition (13.3%), and acute diarrhea (14.1%) and not mutually exclusive.[13] Although this study did not assess causes of death, these results align with our findings around most commonly reported symptoms preceding HEU infant death including diarrhea (22%), difficulty breathing (14.8%), not eating (16.7%), fever (9.3%), and cough; which suggest potential pulmonary or gastrointestinal illness.

During follow-up, 9.6% (n=107) of infants and 6.6% (n=74) of mothers were hospitalized at least once, with a median of 1 visit (IQR: 1–2) for both. Of the 107 hospitalized infants, reported reasons for hospitalization were diarrhea (28.0%), coughing (39.3%), rash (5.6%), and fever (50.5%) and non-mutually exclusive. Infant hospitalization in our analysis was lower than reported in a comparable cohort of HEU infants followed through 20 months age in Malawi in 2008, when ART coverage levels were lower.[17] Although we observed relatively lower hospitalization, there were several commonly reported symptoms preceding death in our study (diarrhea, difficulty breathing, not eating, and cough). Together, these findings suggest potential morbidity in HEU infants that was undiagnosed and/or sub-optimally managed and ultimately resulted in infant mortality.

Although our study offers many strengths including a relatively large number of infants, an observational real-world setting that was conducted in the ART-era, and data that represent a range of potential exposures and outcomes; it also has several main limitations to consider in interpreting our findings. First, we did not have a comparison group of HIV-unexposed infants and therefore were unable to assess how much of the morbidity and mortality we observed is attributable to HIV exposure; however, we were able to compare mortality in our cohort with national statistics on infant mortality in Zimbabwe. Second, we did not have sufficient completeness of data or distribution of events to include several key variables in our analyses, including maternal CD4, immunization status, maternal hospitalization, and

maternal vital status; potentially resulting in residual confounding of our results. Third, given that post-baseline weight was more likely to be available among infants who accessed the health system (either for postnatal care or for hospitalization), our finding of poor growth among HEU infants may not be representative of all HEU infants. Directionality of potential bias that may result is unclear due to the complexity of reasons that may contribute to infants accessing or not accessing the health system. Infants attending postnatal care may have better growth, but sick infants who are hospitalized may have worse growth; similarly, infants too sick to attend the health system may have worse growth, but well-infants, whose caregivers may consequently decide postnatal care is unnecessary, may have better growth. Finally, our study was conducted just prior to adoption of Option B+ and Treat All in Zimbabwe, and therefore, our findings may not be generalizable to HEU infants currently; however, based on our study findings, we would expect that HEU infants currently are born to mothers who are more likely to be on ART prior to, during, and after pregnancy and accordingly, would have better survival.

Despite these limitations, our analysis provides clear evidence that warrants further investigation and clinical program response. In the current area of Option B+ and Treat All, our data suggest that efforts to identify and start women living with HIV pre-delivery may not only prevent HIV transmission to the infant, but also contribute to their survival as HEU infants, which aligns with the PMTCT program HIV-free survival ultimate goal. Our findings of higher mortality among HEU infants not exclusively breastfed early in life and increasingly poor growth during the weaning period leading up to cessation of breastfeeding, underscore the importance of both facility and community-based counseling and support for mothers to breastfeed for as long as needed (and at least for 12 months) to transition to a nutritionally adequate and safe diet for the infant, per updated 2016 WHO guidelines.[18] Our finding of pneumonia- and gastrointestinal infection-like symptoms commonly reported as potential causes of death highlight the need to leverage all opportunities for prevention or early identification and management of childhood illness. Prevention interventions should include cotrimoxazole prophylaxis until cessation of breastfeeding; TB preventative therapy; water, sanitation and hygiene; and routine immunizations. Early identification and management of childhood illness should be offered any time a HEU infant visits a health facility including during early infant diagnosis, routine infant postnatal visit, immunization, and maternal ART appointments. Furthermore, evidence suggests that midwives, community health workers, and informal cadres such as “mentor mothers” and orphan and vulnerable children program case managers, can help to identify HEU infants with signs and symptoms of illness and refer them to the health facility for timely management.[19]

In conclusion, our findings provide additional evidence that HEU infants are vulnerable to morbidity and mortality, but that there are clinical and programmatic opportunities to help address this vulnerability and contribute to HIV-free survival of these infants.

CONFLICTS OF INTEREST AND FUNDING:

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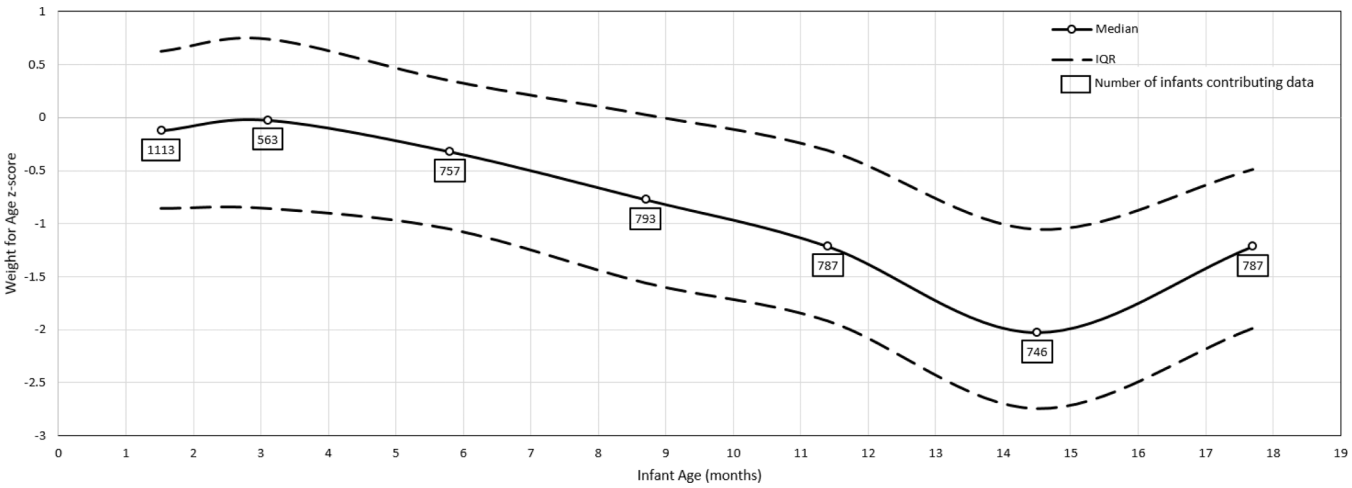
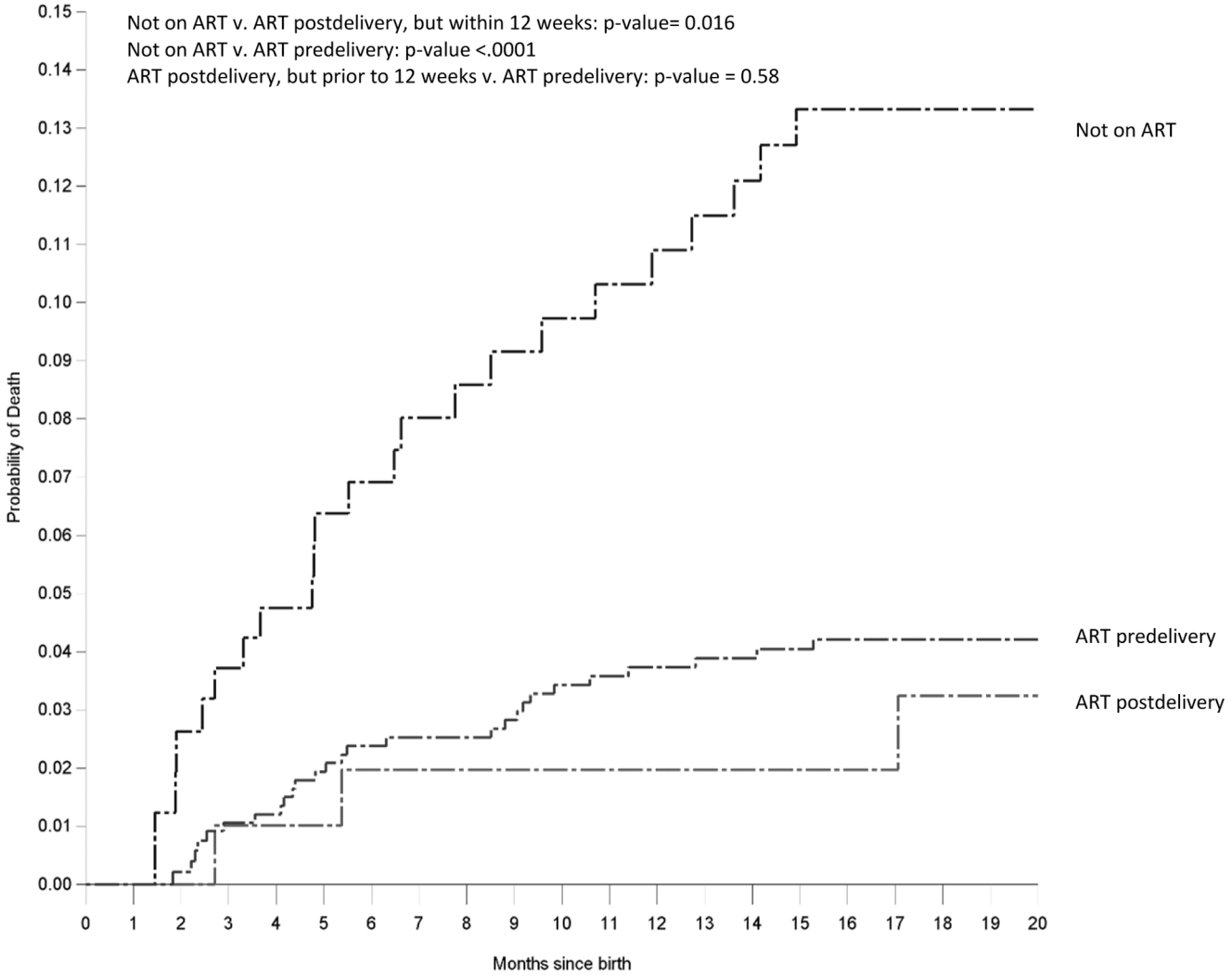


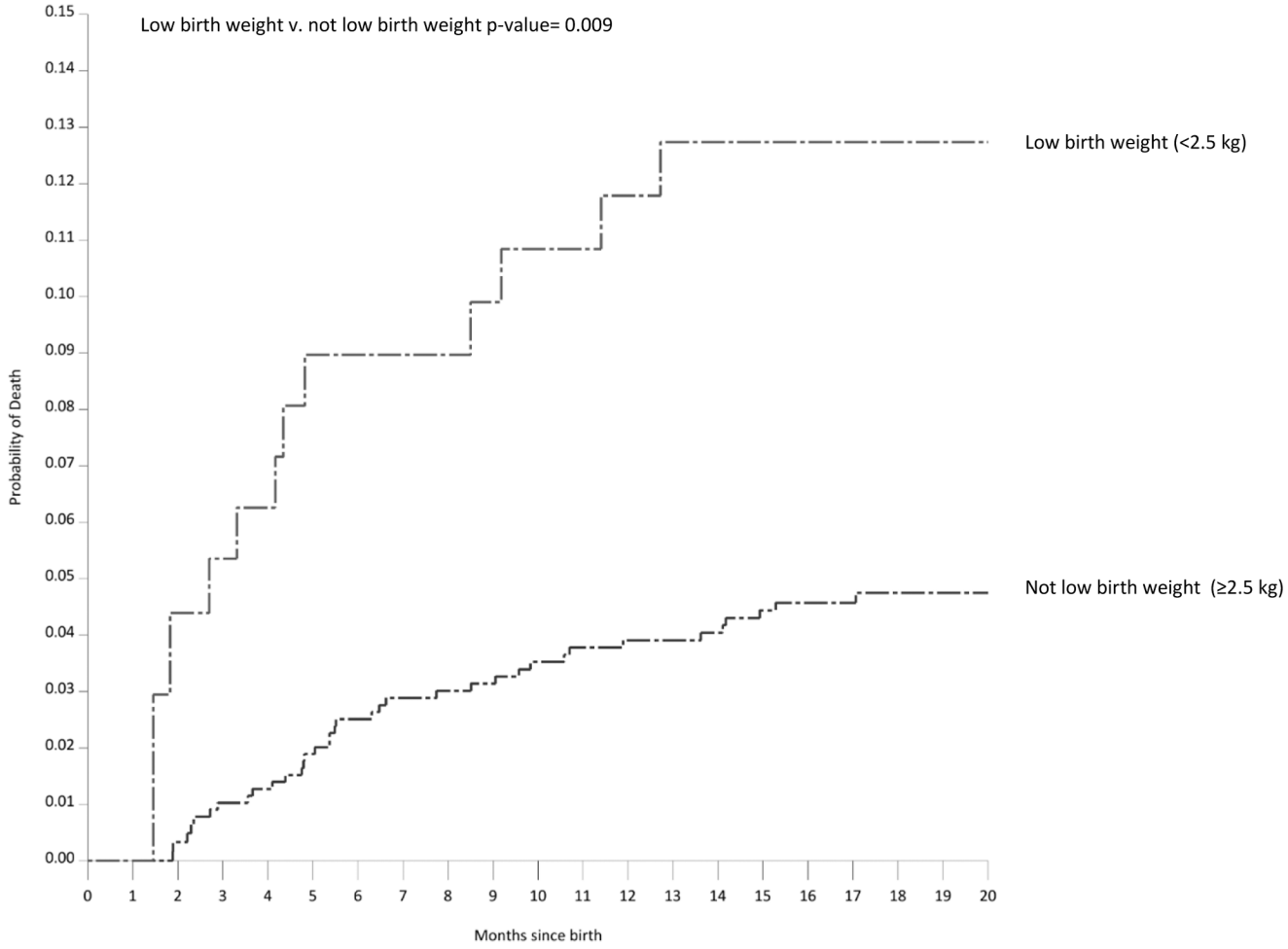
Figure 1.

Median weight-for-age z-scores (WAZ) over time among HIV-exposed uninfected infants, 18-Month Prospective Cohort of a Nationally Representative Sample of Mother–Infant Pairs in Zimbabwe (n=1115)

Panel A



Panel B



Panel C

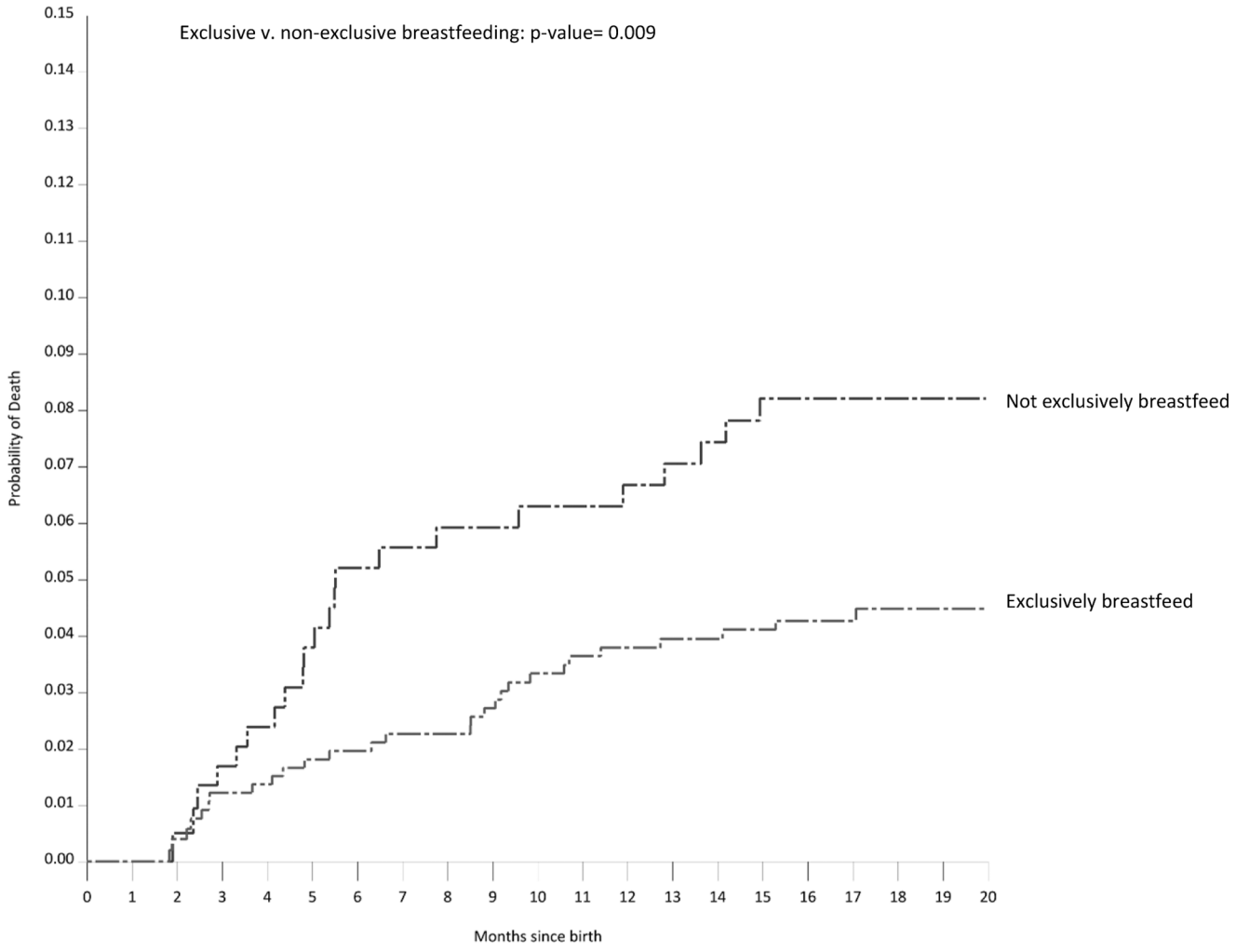


Figure 2.

Cumulative probability of death over time among HIV-exposed uninfected infants by timing of maternal ART, birth weight, and feeding practices 4–12 weeks post-delivery, 18-Month Prospective Cohort of a Nationally Representative Sample of Mother–Infant Pairs in Zimbabwe (n=1115)

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Table 1.

Distribution of baseline characteristics among HIV-exposed uninfected (HEU) infants and their mothers overall, and by mortality status at end of follow-up (n=1115)

	All HEU n=1115 (100%)	HEU dead n=54 (4.8%)	HEU alive n=1061 (95.2%)	p-value[a]
INFANT CHARACTERISTICS				
Infant age at baseline (weeks), median (IQR)	6.6 (6.0–8.9)	6.4 (5.9–7.7)	6.6 (6.0–8.9)	0.42
Infant gender, male	573 (51.4)	29 (53.7)	544 (51.3)	0.87
Female	542 (48.6)	25 (46.3)	517 (48.7)	
Birth weight, low (<2.5 kg)[b]	117 (11.1)	11 (22.9)	106 (10.6)	0.009
not low (≥2.5 kg)	934 (88.9)	37 (77.1)	897 (89.4)	
Delivery location, home[b]	158 (14.3)	11 (21.2)	147 (13.9)	0.25
hospital or clinic	951 (85.8)	41 (78.9)	910 (86.1)	
Mode of transport to clinic, motorized	292 (26.2)	9 (16.7)	283 (26.7)	0.23
Walking	823 (73.8)	45 (83.3)	778 (73.3)	
Feeding practices 0 to 4–12 weeks post-delivery, exclusive breastfeeding[b]	772 (70.3)	28 (53.8)	744 (71.1)	0.020
mixed breastfeeding	301 (27.4)	23 (44.2)	278 (26.6)	
no breastfeeding	25 (2.3)	1 (1.9)	24 (2.3)	
Reported exposure to tuberculosis, yes	239 (21.4)	9 (16.7)	230 (21.7)	0.31
no	876 (78.6)	45 (83.3)	831 (78.3)	
MATERNAL CHARACTERISTICS				
Maternal age, median (IQR)	29 (24–33)	28 (23–33)	29 (24–33)	0.40
Marital status, married or cohabitating	977 (87.6)	48 (88.9)	929 (87.6)	0.79
single, widow, divorced, separated	138 (12.4)	6 (11.1)	132 (12.4)	
Maternal education, < grade 8[b]	398 (35.7)	22 (40.7)	376 (35.5)	0.72
≥ grade 8	716 (64.3)	32 (59.3)	684 (64.5)	
Socio-economic status, low (1st or 2nd quintile)	411 (36.9)	18 (33.3)	393 (37.0)	0.26
higher (3rd, 4th, or 5th quintile)	704 (63.1)	36 (66.7)	668 (63.0)	
Maternal ART status, did not initiate ART	275 (24.7)	24 (44.4)	251 (23.7)	0.001

	All HEU n=1115 (100%)	HEU dead n=54 (4.8%)	HEU alive n=1061 (95.2%)	p-value[a]
initiated ART pre-conception	406 (36.4)	14 (25.9)	392 (37.0)	
initiated ART during pregnancy	327 (29.3)	13 (24.1)	314 (29.6)	
initiated ART post-delivery	107 (9.6)	3 (5.6)	104 (9.8)	
Maternal CD4 count at baseline visit (cells/mm^3)[b], ≤350	394 (47.1)	23 (60.5)	371 (46.4)	0.084
>350	443 (52.9)	15 (39.5)	428 (53.6)	
Gestational age at 1st ANC (weeks), median (IQR)[b]	20 (16–26)	20 (13–25)	20 (16–26)	0.91
Maternal hospitalization since delivery prior to 12 weeks, yes	19 (1.7)	1 (1.9)	18 (1.7)	0.86
no	1096 (98.3)	53 (98.2)	1043 (98.3)	

[a]Differences assessed using two-sided log-rank test.

[b]Missing: maternal education: n=1 (0.9%); birth weight: n=64 (5.7%); delivery location: n=6 (0.5%); feeding practices: n=17 (1.5%); maternal CD4 at baseline: n=278 (24.9%); gestational age ANC1: n=216 (19.4%)

Table 2.

Associations between maternal ART, low birth weight, and infant feeding practices and cumulative mortality among HIV-exposed uninfected infants, 18-Month Prospective Cohort of a Nationally Representative Sample of Mother–Infant Pairs in Zimbabwe (n=1115)

	Crude model HR (95% CI)	Full Model HR (95% CI)[a]	Reduced (final) Model HR (95% CI)[b]
ART pre-delivery v. no ART	0.32 (0.18–0.56)	0.33 (0.17–0.63)	0.26 (0.14–0.47)
ART post-delivery, but within 12 weeks v. no ART	0.23 (0.07–0.76)	0.26 (0.07–0.88)	0.22 (0.07–0.74)
Low birth weight (<2.5 kg) v. not low birth weight (≥2.5 kg)	2.46 (1.25–4.83)	2.77 (1.35–5.71)	2.66 (1.35–5.24)
Exclusive breastfeeding v. mixed feeding/no breastfeeding	0.52 (0.30–0.90)	0.48 (0.26–0.87)	0.47 (0.26–0.84)

[a] adjusted for infant gender, maternal education, infant TB exposure, maternal age, maternal socio-economic status, infant birth weight, hospital delivery (or not), mode of transport to health facility, and infant feeding;

[b] ART timing adjusted for low birth weight, infant feeding and maternal age; low birth weight adjusted for maternal ART timing and maternal age; infant feeding adjusted for low birth weight, and maternal age

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