Causes and Predictors of Mortality among HIV-Exposed Infants in Rural North-Central Nigeria: Results of a Simple Verbal Autopsy Survey

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Abstract

Background HIV-exposed infants (HEI) who die before diagnosis or treatment initiation, or who die in spite of being HIV-free constitute missed opportunities for reducing infant mortality. Verbal autopsy (VA) has been successfully applied in the collection of data to determine symptoms and circumstances surrounding death among infants, children and adults among populations that lack vital registration systems. There is little available data on rates and causes of death among HIV-exposed infants (HEI) in Nigeria. We used VA to characterize attributable causes and predictors of mortality among HEI in rural North-Central Nigeria.

Methods Pregnant women living with HIV and HEI were enrolled at rural primary healthcare facilities and followed-up for 12 months, post-delivery. A simple 21-item VA instrument was used to collect infant mortality information from mothers, other family members, mentor mothers, and/or healthcare workers. Attributable causes of death were determined by physician coding. Multivariate logistic regression was performed to determine independent predictors of mortality.

Results Data from 455 HIV-exposed infected and uninfected fetus/infant-mother pairs were analyzed. All mothers received anti-retroviral therapy. Seventy-five (16.5%) fetuses/infants died during gestation and within 12 months post-delivery. Forty (53.3%) deaths occurred in utero. The 12-month infant mortality risk among HEI in our study was 88.7/1,000. Among the 35 live-born infants, birth asphyxia (6/17, 35.3%) and sepsis (7/18, 38.9%) were the most common causes of death in the neonatal and post-neonatal periods, respectively. Unadjusted estimates showed that a greater proportion of deceased infants had mothers who did not deliver at a health facility (53.3 vs 31.8%, $p=0.003$), and who were newly HIV-diagnosed during pregnancy (69.3 vs 50.8%, $p=0.029$). Infants receiving nevirapine prophylaxis within 72 hours were less likely to have died (aOR = 0.40, 95% CI: 0.2-0.9).

Conclusions Early HIV diagnosis and treatment among women of child-bearing age, maternal access to facility delivery and timely infant antiretroviral prophylaxis should be programmatically strengthened to reduce HEI mortality. Additionally, robust monitoring and evaluation systems are needed to track and record deaths among HEI.

Background

Sustainable Development Goal (SDG) 3 (Good Health and Well-being) aims, by 2030, to reduce neonatal mortality to ≤ 12 per 1,000 live births and under-5 mortality to ≤ 25 per 1,000 live births (1).

Nigeria has high neonatal, infant and under-5 mortality rates of 33, 65 and 100 per 1,000 live births respectively (2). Major causes of child mortality in Nigeria are largely preventable, and mirror those in other resource-limited settings (3). Among neonates, these include prematurity, congenital anomalies, intrapartum complications including birth asphyxia; sepsis, pneumonia, and tetanus (4). Between ages one month and 5 years, major causes of death include pneumonia, diarrhea and malaria, and other communicable, maternal, perinatal and nutritional conditions (4).

In addition to high child mortality, Nigeria has had the highest or second-highest child HIV burden and number of new child HIV infections globally, for over 10 years (5). This necessitated Nigeria's inclusion among 22 priority countries in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (6). Unfortunately, Nigeria posted the lowest decline (21%) in new child HIV infections among Global Plan countries (6) and had an estimated 12,000 AIDS deaths among 0 to 9 year-old children in 2018, the highest globally (7). Nigeria's high child mortality rates, high child HIV prevalence and AIDS-related deaths make SDG 3 of prime importance.

HIV-exposed infants (HEI) who die before determination of HIV status or anti-retroviral therapy (ART) initiation, or who die in spite of being HIV-free constitute missed opportunities for reducing infant mortality in the context of the prevention of mother-to-child transmission of HIV (PMTCT) (8–10). There is little available data on mortality and attributable causes of death specific to HEI in Nigeria. Given Nigeria's high infant mortality and child HIV burden, it is important to obtain this data to guide strategies for reducing infant mortality and improving PMTCT outcomes in line with SDG 3. In resource-limited settings, the challenges of poverty, maternal factors (eg younger age, narrow birth-spacing and non-facility delivery), weak health systems and socio-cultural barriers compound mortality risk among infants, regardless of HIV-exposure (11–13). Unfortunately, health facility-based reports do not comprehensively account for deaths in low and middle-income countries (LMICs), where many people die outside hospital settings without proper documentation (14,15).

Verbal autopsy (VA) is based on interviews with caregivers, next of kin and witnesses to death and interprets these narratives to ascertain causes of death (16). VA is an invaluable method for obtaining information on causes of death in settings with low rates of civil registration and death certification (16). The World Health Organization (WHO) supports VA and has tools that have been used in more than 45 LMICs for different programs and disease entities, among children and adults (15–17). The objective of this study was to determine attributable causes and predictors of death among HEI, regardless of HIV status, using a simple VA approach.

Methods

Data presented in this paper was collected as part of the MoMent (Mother Mentor) study, one of six WHO-supported studies under its INSPIRE (Integrating and Scaling Up PMTCT through Implementation Research) initiative (18). MoMent evaluated the impact of structured maternal peer support on presentation/uptake for early infant diagnosis (EID) and maternal retention in care among women living with HIV and their HEI (19–21).

Study Design and Setting

MoMent was a prospective cohort study conducted in rural and semi-rural communities of the Federal Capital Territory and Nasarawa State in North-Central Nigeria. Twenty primary healthcare centers were selected and pair-matched based on facility profile data. Ten intervention sites provided maternal peer support delivered in a structured program comprising closely-supervised, trained mentor mothers using

standardized tools; 10 control sites delivered routine peer support from peer counselors with little to no training, tools or supervision (19,21).

Participant Recruitment

Between 2014 and 2017, pregnant women living with HIV (WLHIV) aged ≥ 15 years were enrolled and followed-up along with their HEI, until 12 months post-delivery. Women in both study arms had access to antenatal HIV testing, continued/prompt initiation of ART, Option B PMTCT regimens, infant feeding counseling, EID, and infant referral for ART if diagnosed HIV-positive (19,20). Detailed descriptions of participant recruitment have been previously published (19–22).

Ethical Considerations

The study was approved by the Nigerian National Health Research Ethics Committee, the Ethics Review Committee of the World Health Organization, and the Institutional Review Board of the University of Maryland, Baltimore. Written informed consent was obtained from all study participants, including parental/guardian consent for infants.

Instrument Adaptation, Data Collection, and Coding

Data on fetal and infant mortality was collected within 6 months of death. Data sources were interviewees connected/related to the infant, including enrolled mothers, other relatives, and healthcare providers including mentor mothers. Documentation, including formal diagnoses regarding infant deaths, were generally not available in facility records (23).

Mortality information was collected using a simple 21-item form (See Appendix). MoMent's VA form was developed and reviewed by a team of clinicians, researchers and public health personnel with extensive local and research experience in HIV/PMTCT. Questions deemed relevant to circumstances surrounding HEI infant mortality and the study setting were put forth. MoMent's VA process had to be simplified for the following reasons:

VA was implemented within a study collecting extensive data from WLHIV and HEI;

VA data was collected as a non-primary objective;

VA collected mortality data among a highly-stigmatized, HIV-affected population in largely rural areas-thus there was concern that multiple probing questions may potentially cause interviewees to withdraw;

VA data was collected by trained lay (non-healthcare worker) staff. Also, most VA interviews had to be verbally translated from English to local Hausa language, which was laborious;

Some study communities were either very hard to reach or had unpredictable periods of insecurity (24).

Thus, questionnaires had to take a relatively short amount of time for completion and for staff to return to safety before nightfall.

Categorization of deaths and attributable causes were performed via physician coding. First, timing of fetal and infant deaths were categorized according to WHO specifications: miscarriage (< 22 weeks' gestation), stillbirth (≥ 22 weeks' gestation to birth), neonatal deaths (birth to < 28 days) and postnatal deaths (≥ 28 days to 12 months) (25). Thereafter, signs and symptoms reported in the VAs were independently reviewed

and assigned a cause of death by three pediatricians. Discrepancies were resolved with repeat reviews and by group consensus. Where an attributable cause of death could not be assigned, it was labeled “not otherwise specified”. Mortality risk was calculated as number of infant deaths per 1,000 live births.

Data Analysis

Descriptive statistics were presented as percentages for categorical variables. Bivariate analysis was conducted using chi-square tests to determine unadjusted comparison of infant and mothers’ characteristics across HEI mortality status. Covariates with p-values ≤ 0.2 in the unadjusted model were considered theoretically relevant for inclusion in the multivariate model.

To determine independent predictors of mortality among HEI, multivariate logistic regression was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Out of 497 pregnant WLHIV enrolled, delivery information was available for 445 (89.5%). These 445 women were pregnant with a total of 455 infants, including 10 sets of twins; 415 (91.5%) infants were live-born (Fig. 1) (8,26).

[Fig. 1. Mortality Outcomes of Infant Cohort in MoMent Study]

At the end of the 12-month post-delivery follow-up period, 75 (16.5%) deaths were recorded among the 455 HIV-exposed fetuses/infants. Forty (53.3%) deaths occurred in utero while 35 (46.7%) were among live-born infants (Fig. 1). Among the 35 live-born infants who died, HIV status was available for 15 (42.9%), out of which seven (46.7%) had a positive result.

Attributable Causes of Death among HIV-Exposed Infants

Given the paucity of relevant clinical and VA data available and the lack of sophisticated diagnostics required, the vast majority of in utero HEI deaths could not be analyzed for cause. However, birth asphyxia and sepsis were the single most common attributable causes of neonatal and post-neonatal death respectively (Table 1).

Table 1
Time and Causes of Fetal and Infant Death Determined by Adapted Verbal Autopsy, N = 75

Time of Death	n (%) ^a	Cause of Death	n (%) ^b
Miscarriage (< 22 weeks' gestation)	7 (9.3)	Miscarriage NOS Anencephaly	6 (85.7) 1 (14.3)
Stillbirth (≥ 22 weeks' gestation to birth)	33 (44.0)	Stillbirth NOS	33 (100.0)
Neonatal (Birth to < 28 days) ^c	17 (22.7)	Birth asphyxia Neonatal death NOS Sudden infant death Neonatal jaundice Sepsis Small for gestational age	6 (35.3) 5 (29.4) 2 (11.8) 2 (11.8) 1 (5.9) 1 (5.9)
Post-neonatal (≥ 28 days to 12 months)	18 (24.0)	Sepsis Post-neonatal death NOS Severe malaria Tetanus Diarrheal disease Hypernatremia	7 (38.9) 6 (33.3) 2 (11.1) 1 (5.6) 1 (5.6) 1 (5.6)
NOS: not otherwise specified			
^a Column percentage; denominator of all 75 fetal/infant deaths			
^b Row percentage; denominator of all deaths in "time of death" category only			
^c Includes n = 10 early neonatal deaths between birth and < 7 days			
Characteristics of Pregnant Mothers and Infants			

[Table 1. Time and Causes of Fetal and Infant Death Determined by Verbal Autopsy, N = 75]

The calculated mortality risk for MoMent's 415 live births was 88.7/1,000. Mortality risk in the neonatal and post-neonatal periods were determined to be 45.6 and 43.2 per 1,000 live births respectively.

Characteristics of Pregnant Mothers and Infants

[Table 2. Maternal-Infant Baseline and Mortality Related Data]

Table 2
Maternal-Infant Baseline and Mortality Related Data

Maternal Data, N = 445^a	N	%
Type of Peer Support		
Routine 189 41.5		
Structured (Mentor Mother) 266 58.5		
Age (Years)		
< 21	44	9.9
21–30	317	71.2
≥ 31	84	18.9
Marital status (Divorced, separated, widowed)		
Single	23	5.2
Married	421	94.6
Missing	1	0.2
Education		
< Secondary	217	48.8
≥ Secondary	228	51.2
Facility delivery		
Yes	277	62.3
No	168	37.7
Employment status		
Employed	130	29.2
Unemployed	315	70.8
Religion		
Christian	148	33.3
Muslim	297	66.7
HIV diagnosis status		
Newly diagnosed	264	59.3
Previously diagnosed	180	40.4

Maternal and Infant Correlates of Mortality among HIV-Exposed Infants

Maternal Data, N = 445^a	N	%
Missing	1	0.2
ART regimen		
Efavirenz-based	300	67.4
Nevirapine-based	135	30.3
Protease inhibitor-based	10	2.2
Mode of delivery		
Spontaneous vaginal	416	93.5
Caesarian section	18	4.0
Instrument-assisted	2	0.4
Missing data	9	2.0
Attendant at delivery		
Unskilled Birth Attendant	134	30.1
Skilled Birth Attendant	309	69.4
Missing data	2	0.4
Outcome at 12 months post-delivery		
Alive	446	98.0
Dead	8	1.8
Missing data	1	0.2
HIV-Exposed Fetus/Infant Data		
Mortality within 12 months of life (N = 455 ^b)		
Alive	346	76.0
Dead	75	16.5
Missing data	34	7.5
Place infant died/confirmed dead (N = 75 ^c)		
Health facility	26	34.7
Home	39	52.0
Other	5	6.7

Maternal and Infant Correlates of Mortality among HIV-Exposed Infants

Maternal Data, N = 445^a	N	%
Missing data	5	6.7
Gender (N = 415 ^d)		
Female	184	44.3
Male	224	54.0
Missing	7	1.7
Birth weight (N = 415 ^d)		
< 2.5 kg	39	9.4
≥ 2.5 kg	245	59.0
Missing data	131	31.6
Nevirapine given within 72 hrs (N = 415 ^d)		
No	68	16.4
Yes	298	71.8
Missing data	49	11.8
HEI: HIV exposed infant; ART: Antiretroviral Therapy ^a Represents all women with delivery data ^b Represents all expected infants from the 445 pregnant women with delivery data (includes 10 sets of twins) ^c Represents all infants who died in utero or post-delivery. Out of 10 sets of twins, 1 twin from two sets died; ie 2 of 20 twins died. ^d Represents all live-born infants		
Maternal and Infant Correlates of Mortality among HIV-Exposed Infants		

Maternal socio-demographic and clinical data at study enrollment is presented in Table 2, in addition to infant birth and mortality data. Approximately 60% of mothers were newly-diagnosed with HIV. Nearly two-thirds (62.3%) delivered at a health facility, and the vast majority (93.5%) delivered vaginally, with 30% of all deliveries attended to by unskilled personnel. Eight women had died within the follow-up period.

Among the 75 fetuses/infants who died, a slight majority (n = 39, 52%) were identified dead at home.

Maternal and Infant Correlates of Mortality among HIV-Exposed Infants

[Table 3. Correlates of HIV-Exposed Infant Mortality: Bivariate Analysis]

Table 3
Correlates of HIV-Exposed Infant Mortality: Bivariate Analysis

HEI Mortality, N = 455						
	Living (N = 380)		Dead (N = 75)		Total	P-Value
Maternal Data ^a	n	%	n	%	n	
Type of Peer Support						
Routine	130	34.2	28	37.3	158	0.983
Structured (Mentor Mother)	217	57.1	47	62.7	264	
Missing ^b	33	8.7	0	0.0	33	
Age (Years)						
< 21	36	9.5	6	8.0	42	0.696
21–30	242	63.7	56	74.7	298	
≥ 31	68	17.9	13	17.3	81	
Missing ^b	34	8.9	0	0.0	34	
Marital status						
Single ^c	17	4.5	5	6.7	22	0.522
Married	328	86.3	69	92.0	397	
Missing ^b	35	9.2	1	1.3	36	
Education						0.665
< Secondary	171	45.0	35	46.7	206	
≥ Secondary	175	46.1	40	53.3	215	
Missing ^b	34	8.9	0	0.0	34	

p values at alpha significance level < 0.05 HEI: HIV exposed infant; ART: Antiretroviral Therapy

^aRepresents all pregnant women (N = 445) with delivery data

^bProportions of missing data are not included in statistical analysis

^cSingle: divorced, separated, or widowed

^dRepresents all expected infants (includes 10 sets of twins) from the 445 pregnant women with delivery data

^eIncludes missing values for fetuses/infants due to in utero or early post-delivery death

HEI Mortality, N = 455						
Facility delivery						
Yes	226	59.5	35	46.7	261	0.003
No	121	31.8	40	53.3	161	
Missing ^b	33	8.7	0	0.0	33	
Employment status						
Employed	102	26.9	20	26.7	122	0.626
Unemployed	244	64.2	55	73.3	299	
Missing ^b	34	8.9	0	0.0	34	
Religion						
Christian	229	60.3	54	72.0	283	0.316
Muslim	118	31.0	21	28.0	139	
Missing ^b	33	8.7	0	0.0	33	
HIV diagnosis status						
Newly diagnosed	193	50.8	52	69.3	245	0.029
Previously diagnosed	154	40.5	23	30.7	177	
Missing ^b	33	8.7	0	0.0	33	
ART regimen						0.025
Efavirenz-based	225	59.2	60	80.0	280	
Nevirapine-based	112	29.5	15	20.0	121	
Protease inhibitor-based	10	2.6	0	0.0	10	

p values at alpha significance level < 0.05 HEI: HIV exposed infant; ART: Antiretroviral Therapy

^aRepresents all pregnant women (N = 445) with delivery data

^bProportions of missing data are not included in statistical analysis

^cSingle: divorced, separated, or widowed

^dRepresents all expected infants (includes 10 sets of twins) from the 445 pregnant women with delivery data

^eIncludes missing values for fetuses/infants due to in utero or early post-delivery death

HEI Mortality, N = 455						
Missing ^b	33	8.7	0	0.0	44	
Mode of delivery						0.004
Spontaneous vaginal	329	86.6	63	84.0	392	
Caesarian section	14	3.7	5	6.7	19	
Instrument-assisted	0	0.0	2	2.6	2	
Missing ^b	37	9.7	5	6.7	42	
Attendant at delivery						0.023
Unskilled Birth Attendant	96	25.3	30	40.0	126	
Skilled Birth Attendant	251	66.1	43	57.4	294	
Missing ^b	33	8.7	2	2.6	35	
Outcome at 12 months post-delivery						0.000
Alive	345	90.7	68	90.7	402	
Dead	2	0.5	6	8.0	8	
Missing ^b	33	8.7	1	1.3	45	
HIV-Exposed Fetus/Infant Data N = 455 ^d	Living (N = 380)		Dead (N = 75)		Total	
	n	%	n	%	n	
Gender						0.390
Female	159	41.8	22	29.3	181	
Male	185	48.7	33	44.0	218	
Missing ^{b,e}	36	9.5	20	26.7	56	

p values at alpha significance level < 0.05 HEI: HIV exposed infant; ART: Antiretroviral Therapy

^aRepresents all pregnant women (N = 445) with delivery data

^bProportions of missing data are not included in statistical analysis

^cSingle: divorced, separated, or widowed

^dRepresents all expected infants (includes 10 sets of twins) from the 445 pregnant women with delivery data

^eIncludes missing values for fetuses/infants due to in utero or early post-delivery death

HEI Mortality, N = 455						
Infant birth weight						
< 2.5 kg	34	8.9	9	12.0	43	0.434
≥ 2.5 kg	224	58.9	43	57.3	267	
Missing ^{b,e}	122	32.1	23	30.7	145	
Infant nevirapine given within 72 hrs						0.006
No	61	16.1	16	21.3	77	
Yes	273	71.8	51	68.0	324	
Missing ^{b,e}	46	12.1	8	10.7	54	
p values at alpha significance level < 0.05 HEI: HIV exposed infant; ART: Antiretroviral Therapy						
^a Represents all pregnant women (N = 445) with delivery data						
^b Proportions of missing data are not included in statistical analysis						
^c Single: divorced, separated, or widowed						
^d Represents all expected infants (includes 10 sets of twins) from the 445 pregnant women with delivery data						
^e Includes missing values for fetuses/infants due to in utero or early post-delivery death						

In Table 3, unadjusted estimates show a greater proportion of deceased infants whose mothers did not deliver at a health facility (53.3 vs 31.8%, $p = 0.003$), and were newly- diagnosed with HIV (69.3 vs 50.8%, $p = 0.029$). Additionally, significantly greater proportions of infants who died had mothers on efavirenz-based regimens, were born by cesarean or instrument-assisted delivery, had unskilled birth attendants, and had mothers who themselves died during follow-up. There were no differences between dead and living infants regarding maternal age, marital/employment status, or educational level. There were also no differences with regard to infant gender, birthweight, or receipt of nevirapine prophylaxis within 72 hours.

Multivariate logistic regression analysis results are presented in Table 4.

Table 4
Predictors of HIV-Exposed Infant Mortality: Multivariate Analysis

	aOR	95% CI		p value
Attendant at delivery				
Unskilled Birth Attendant (Ref)				0.646
Skilled Birth Attendant	1.3	0.5	3.4	
Facility delivery				
No (Ref)				0.194
Yes	0.5	0.2	1.3	
Maternal education				
No (Ref)				0.669
Yes	0.8	0.4	1.6	
Maternal employment status				
Unemployed (Ref)				0.972
Employed	1.1	0.6	2.1	
Age (years)				
< 21 (Ref)				
21–30	1.9	0.5	6.5	0.419
≥ 31	1.8	0.5	7.2	0.514
Infant gender				
Female (Ref)				0.460
Male	1.3	0.7	2.5	
Birth weight				
< 2.5 kg (Ref)				0.578
≥ 2.5 kg	0.8	0.3	1.9	
Infant nevirapine given within 72 hrs				
No (Ref)				0.023
Alpha significance level ≤ 0.05, aOR = adjusted odds ratio, CI = confidence interval.				
Covariates included in multivariate model: maternal age, employment status, education, and infant gender and birth weight.				

	aOR	95% CI	p value
Yes	0.4	0.2	0.9
Alpha significance level ≤ 0.05 , aOR = adjusted odds ratio, CI = confidence interval.			
Covariates included in multivariate model: maternal age, employment status, education, and infant gender and birth weight.			

[Table 4. Predictors of HIV-Exposed Infant Mortality: Multivariate Analysis]

After adjusting for possible confounding factors in multivariate analysis (Table 4), only provision of infant nevirapine was found to correlate with infant mortality: compared to infants not receiving nevirapine or receiving it late, infants receiving nevirapine within 72 hours were less likely to die during follow-up (aOR = 0.40, 95% CI: 0.2–0.9).

Discussion

This study reports on HEI mortality and attributable causes and predictors in rural North-Central Nigeria. VA remains an important approach for reporting causes of death in resource-limited and/or unstable settings where mortality records may be absent or poorly maintained (14–16). Among the modest number of published reports on specific causes of mortality among African HEI, few have been from the post-ART/-PMTCT scale up era, and fewer still from rural settings where VA may be most applicable for data collection (27–38). To date, there is little available data on causes of death, determined by VA or otherwise, among HEI in Nigeria.

The 12-month infant mortality risk among HEI in our study (88.7/1,000) was higher than the national infant mortality rate of 65/1,000 (2). Our study was unable to tease out whether transmitted HIV infection or the state of being HIV-exposed were direct causes or contributing factors to in- and ex utero deaths, however we postulate a high likelihood that this is the case: prior studies report higher mortality rates among HIV-exposed uninfected infants compared to non-HIV exposed infants (35,39–42). The mortality risk results should however be interpreted with caution given our relatively small sample size. Additionally, we were unable to confirm HIV status among 20 of 35 live-born infants who died; availability of those results could have influenced our conclusions with respect to contribution of HIV infection to mortality in our cohort.

In utero deaths accounted for slightly more than half of infant deaths (53.3%) in our cohort. However, due to constraints in availability of sophisticated diagnostics and our VA approach, causes of intra-uterine death could not be ascertained. That being said, the lack of relatively simple routine prenatal syphilis testing for pregnant women in our cohort was a major missed opportunity, as syphilis is a significant cause of stillbirth globally (43). Dual HIV-syphilis testing and subsequent treatment for women found positive for one or both conditions is important for disease control and infant survival, particularly in sub-Saharan Africa (44). Birth asphyxia and sepsis were the most common attributable causes of neonatal and post-neonatal death respectively. Infectious and respiratory diseases have been reported as the major causes of death among

HEI in low-resource, high-burden countries (45). Specifically, pneumonia, diarrhea, septicemia and malnutrition have been reported as the most common causes of death among HEI in sub-Saharan Africa (27–39). Our study agrees with previous HEI mortality studies, which report diarrhea, birth asphyxia/perinatal conditions and sepsis as major causes of death among HIV-exposed infants and children under 24 months (28,35,46,47). These studies also cite acute respiratory infection and malnutrition as major causes of HEI death, however our VA approach was unable to determine these outcomes for our cohort.

Bivariate analysis correlated the following with HEI mortality: non-facility delivery, new maternal HIV diagnosis, maternal efavirenz-based regimen assisted delivery, unskilled birth attendant, post-partum maternal death and infant's non-receipt of nevirapine prophylaxis within 72 hours of life. Several studies support our findings of non-facility delivery, new maternal HIV diagnosis, maternal efavirenz, non-vaginal delivery, unskilled birth attendant, post-partum maternal death as correlates of HEI mortality (32,34,38,48). In our study however, only non-receipt of infant nevirapine within 72 hours persisted as a correlate of HEI mortality in multivariate analysis.

The independent predictive value of non-/or late receipt of nevirapine prophylaxis and infant mortality in our study is not unexpected. Timely receipt within 72 hours of birth and completion of at least 6 weeks of infant antiretroviral prophylaxis has been shown to reduce HIV transmission to HEI during gestation, delivery and breastfeeding (49–53). This evidence is reflected in the WHO (54) and Nigerian guidelines (55) for infant antiretroviral prophylaxis in PMTCT. As such, infants who did not receive prophylaxis or received it later than recommended will be at higher risk for HIV transmission and subsequently, mortality, particularly if ART initiation is delayed or missed. However, given that some of the deceased infants were HIV-free, the correlation of late/non-receipt of infant prophylaxis with mortality may point to more global issues in the HEI's life or family/environment, such as poor health-seeking behavior, poverty, poor knowledge, or concurrent but unmeasured risks of mortality related or unrelated to maternal and/or infant HIV infection. Unfortunately, there are currently few published studies specifically investigating or reporting on non-/late receipt of antiretroviral prophylaxis as a predictor of HEI mortality.

Our study showed no significant association between the MoMent study's structured mentor mother support intervention and infant survival. While there is ample evidence on the positive impact of maternal peer support on maternal PMTCT retention, adherence and viral suppression, EID timeliness/uptake, and rate of vertical transmission in Nigeria (20,21) and in sub-Saharan Africa and globally (56–62), few studies explicitly report on its direct impact on HEI mortality. This may be due largely to sample size constraints; studies conducted so far-including ours- may not have been powered enough to investigate this.

A robust PMTCT program should be comprehensive and integrated with maternal, neonatal and child healthcare and goals. This should include dual antenatal HIV/syphilis testing of pregnant women, maternal access to facility delivery, timely initiation of maternal treatment and infant prophylaxis where relevant, early diagnosis and treatment of infant HIV and other perinatal and infectious diseases such as birth asphyxia, sepsis and pneumonia, that contribute to early infant mortality. Simplified VA approaches combined with strengthened monitoring and evaluation could improve the availability and quality of data on HEI mortality

and contribute to feasible and sustainable approaches to management reducing mortality among HEI in high HIV-burden, resource-limited settings.

Study Limitations

Our study is not without limitations. The generalizability of our VA approach in determining cause of death is not confirmed. This is partly due to lack of prior comparative data (VA or otherwise) and an unavailable “gold standard” such as clinical/laboratory diagnosis for determining cause of death among HEI in our largely rural study setting. Thus, bias is introduced by inaccuracies from wrong reporting, wrong causes of death ascribed, and absence of an established diagnosis reflected by the high number of “not otherwise specified” cases.

Unfortunately, the unavailability of complete data on HIV test results limited the analysis of HIV-positive status as a predictor of (in- or ex-utero) infant mortality. Malaria is a significant cause of infant mortality in our study setting (12,13,63); our VA approach may have underestimated malaria-related mortality in our cohort.

Another limitation is non-collection of data on infant feeding status at time of death to analyze as a predictor of mortality. A study conducted in India among HIV-exposed infant found that mixed feeding and animal milk substitute are important factors responsible for high rates of gastroenteritis, which in turn contributed to infectious hospitalization and in-hospital mortality (64). As previously mentioned, the non-availability of maternal syphilis testing was a missed opportunity for infant mortality analysis, specifically for stillbirths.

Conclusions

Despite progress made in PMTCT globally, mortality rates remain high among infants born to women living with HIV in sub-Saharan Africa. The gains made in the prevention of vertical HIV transmission should be concurrent with significant reductions in all-cause mortality among HIV-exposed infants. In order to fully achieve the goal of HIV-free survival for HIV-exposed infants, integrated, evidence-based maternal-child health and PMTCT strategies are needed to mitigate HIV-related and un-related causes of mortality in this population.

Declarations

Ethics approval and consent to participate: The MoMent study was approved by the Nigerian National Health Research Ethics Committee, the Ethics Review Committee of the World Health Organization and the Institutional Review Board of the University of Maryland, Baltimore. All study participants provided written informed consent; infant consent was provided for by one parent or legal guardian.

Consent for publication: Not applicable.

Competing interests: The authors have no conflicts of interest to disclose.

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Authors' contributions: CEO drafted the manuscript and contributed to data analysis/interpretation. SE contributed to study implementation, data acquisition/analysis/interpretation and manuscript drafting. EEC contributed to data analysis/interpretation and manuscript drafting. TLJ contributed to manuscript drafting and critical review. GN and MB contributed to data acquisition and critical review of the manuscript. JBN and EWI contributed to data analysis and interpretation, and critically reviewed the manuscript. NASA conceptualized and designed the study and contributed to study implementation, data acquisition/analysis/interpretation and drafting/critical review of the manuscript. All authors read and approved the final manuscript.

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Data Accessibility: All data relevant to this publication have been reported and/or submitted as part of this article.

Appendix: MoMent Deceased Infant Verbal Autopsy Form

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Figures

Fig. 1. Mortality Outcomes of Infant Cohort in MoMent Study

Figure 1

Mortality Outcomes of Infant Cohort in MoMent Study

Supplementary Files

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