Infectious Morbidity, Mortality and Nutrition in HIV-exposed, Uninfected, Formula-fed Infants

Results From the HPTN 040/PACTG 1043 Trial

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Background: HIV-exposed uninfected (HEU) infants are a growing population with potentially poor health outcomes. We evaluated morbidity and mortality in HEU formula-fed infants enrolled in the NICHD HPTN 040/PACTG 1043 trial.

Methods: Infectious morbidity, mortality and undernutrition were evaluated within a cohort of 1000 HEU infants enrolled between April 2004 and April 2010 in Brazil (n = 766) and South Africa (n = 234) as part of the NICHD/HPTN 040 trial of 3 different antiretroviral regimens to decrease intrapartum HIV vertical transmission.

Results: Twenty-three percent of infants had at least 1 infectious serious adverse effect. Infants born to mothers with <12 years of education [adjusted odds ratio (AOR), 2.6; 95% confidence interval [CI], 1.2–5.9), with maternal viral load of >1,000,000 copies/mL at delivery (AOR, 9.9; 95% CI, 1.6–63.1) were more likely to have infectious serious adverse effects. At 6 months, the infant mortality rate per 1000 live births overall was 22 ± 2.6, 9.1 ± 1.8 in Brazil and 64.1 ± 3 in South Africa. Undernutrition and stunting peaked at 1 month of age with 18% having a weight-for-age Z score ≤−2, and 22% with height for Z score ≤−2. The likelihood of infant mortality was greater among infants born in South Africa compared with Brazil (AOR, 6.2; 95% CI, 2.5–15.8), high maternal viral load (AOR, 1.7; 95% CI, 1.01–2.9) and birth weight-for-age Z score ≤−2 (AOR, 5.2; 95% CI, 1.8–14.8).

Conclusions: There were high rates of undernutrition, stunting and infectious serious adverse effect in this study's formula-fed HEU population. Suppressing maternal HIV viral load during the peripartum period may be a modifiable risk factor to decrease infant mortality.

Key Words: HIV exposed, uninfected infants, formula feeding, undernutrition

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Each year, an estimated 1.5 million HIV-infected women give birth in low- and middle-income countries.[1] Approximately, 25%–45% of infants born to HIV-infected mothers will become infected without appropriate interventions to prevent mother-to-child transmission (PMTCT). HIV-infected infants have high morbidity and mortality without prompt initiation of treatment.[2] However, a number of studies have suggested that HIV-exposed uninfected (HEU) children may also face an increased risk of serious infections and mortality compared with HIV-unexposed infants, while other data do not support this association.[3–12] The etiology for possible increased morbidity and mortality in HEU infants is likely multifactorial, including immunologic abnormalities[13–16] and lack of parental care,[17] but some authors postulate that lack of breast-feeding by HIV-infected mothers may contribute to this poor outcome.[18–23] In HEU infants born in Africa, breast-feeding is associated with decreased rates of infectious morbidity, including pneumonia[3,24,25] and gastroenteritis,[26] as well as decreased mortality.[27] However, other studies performed in South Africa and Kenya have suggested that there is no difference in morbidity and mortality if there is access to clean water,[28,29] and recent data suggest a trend toward worse outcomes in HEU infants even when they are breast-fed.[8] Furthermore, it has been well documented

that breast-feeding can result in HIV transmission.[30] Discouraging breast-feeding for HIV-infected women presents a dilemma in many developing countries if HEU infants succumb to complications unassociated to HIV but related to formula-feeding.

Given that this is an area of uncertainty and continued investigation, the World Health Organization (WHO) and in-country PMTCT policies are constantly evolving. In low- and middle-income countries, the WHO now recommends that all new mothers on antiretroviral therapy (ART) can breast-feed for 12 months or longer.[31] South Africa's national policy largely mirrors the WHO recommendations, but the country also provided free formula to HIV-infected women until 2011.[32] In contrast, Brazilian policies recommend formula-feeding regardless of maternal ART because background infant morbidity and mortality from infections are low, and even small increases in the potential for HIV transmission are unacceptable.[33]

Given this backdrop, the present study's objective was to evaluate HEU formula-fed infants born to a high-risk population of mothers who were enrolled in a large HIV PMTCT trial for infectious serious adverse events (ISAEs), undernutrition, stunting and mortality during their first 6 months of life.

MATERIALS AND METHODS

We performed an analysis of data collected as part of the NICHD/HPTN 040 (P1043) study,[34] which enrolled HIV-infected mothers who had not received antiretroviral drugs before labor because of late presentation for medical care or because HIV testing was not performed during pregnancy. Enrollment and infant follow-up for 6 months occurred between April 2004 and January 2011 with primary results published in June 2012. Because the main study endpoint was the comparative efficacy of different infant antiretroviral regimens to prevent intrapartum HIV transmission, the study was designed exclusively for formula-fed infants, and formula was provided to all participants. All households had access to clean water. Enrollment occurred at 17 sites in Brazil, South Africa, Argentina and the United States. The study was approved by local and collaborating institutional review boards.

In this analysis, we included all HEU infants who completed 6 months of study follow-up in a selection pool along with live-born HIV-exposed infants who died before the 6-month follow-up study visit and who had negative HIV polymerase chain reaction results before death. We excluded infants diagnosed with HIV infection, lost to follow-up before 6 months of age or who had any evidence of breast-feeding during the study period. From this selection pool, we included 1000 infants to perform this analysis initially as part of the Data Safety Monitoring Board recommendations, using a systematic sampling method by study site to guarantee all sites were represented proportionately and infants were selected over the range of time that the study had been in operation. Given that 97.5% of recruitment for the parent study occurred in Brazil and South Africa, we limited this analysis to participants from these 2 countries.

Study visits occurred at birth, 4 to 7 days, 10 to 14 days, 4 to 6 weeks, 3 months and 6 months of age. Medical histories were obtained and physical examinations were performed at each visit. Infant gestational age was estimated based on maternal report of last menstrual period. Prenatal ultrasound results, if available, were also used to help verify gestational age. If neither were available, the site principal investigator estimated the infant's age using the Ballard and Dubowitz scores.

Infants' weight and length were measured at each visit and plotted using the WHO growth charts for each sex. All sites received monitoring visits, periodic trainings and were supervised on taking infant measurements using an adaptation of the WHO "Measuring a Child's Growth."[35] All equipment, including scales, used in the study were checked and rechecked throughout study period with extensive training delivered to site staff for technical procedures such as measuring weight, height and vital signs. Infants with weight-for-age Z score (WAZ) ≤ -2 and > -3 were considered moderately undernourished, and those with WAZ ≤ -3 were considered severely undernourished. Infants with height-for-age Z score (HAZ) ≤ -2 and > -3 were considered moderately stunted, and those with HAZ ≤ -3 were considered severely stunted. All ISAEs were documented, including congenital infections and infections involving the respiratory system, the gastrointestinal system and the central nervous system requiring medical care (grade 3), deemed as life-threatening (grade 4) or resulting in death (grade 5). Cause of death was documented on case report forms completed by site principal investigators. Complete blood counts and hepatic aminotransferase levels were measured at all visits except at 6 months. Serious adverse events were graded with the use of the 1993 Division of AIDS Toxicity Tables for Grading Severity of Pediatric Adverse Experiences.[36]

At study enrollment, mothers were interviewed about risk behaviors, including illegal substance use, alcohol use, tobacco use and receipt of prior prenatal care. Maternal HIV RNA levels, CD4+ T-lymphocyte (CD4) cell subsets and serologic tests for syphilis were obtained at the time of labor/delivery. Infant data included mode of delivery, birth weight, gestational age, HIV antiretroviral prophylaxis arm and whether zidovudine was received during the intrapartum period by the mother.

Statistical Analysis

Two-sample t test and χ^2 test were used to compare the differences in continuous and categorical variables between 2 independent samples (as appropriate). Univariate and multivariate logistic regression analyses were performed to assess the relationship of potential predictors with infants having at least 1 ISAE and with infant mortality. To explore potential risk factors in relation with ISAE and with infant mortality in Brazil and South Africa separately, a stratified logistic regression was performed by infant's birth country. Covariates with a type III overall P value <0.15 from univariate models were entered into initial full multivariable model for model selection. Backward, forward and stepwise model selections were used to select the best final multivariable model. In particular, for the ISAE analysis, birth country, race, years of education, viral load and WAZ at birth were included in the initial full multivariate model for model selection. For infant mortality analysis, birth country, gestational age at delivery, race, whether the mother received any prenatal care during pregnancy, mode of delivery, viral load and WAZ at birth were included in the initial full model for model selection. When viral load was less than 400 copies/mL, value was imputed to be 200 copies/mL and considered as undetectable. All computations were done using SAS version 9.3.

RESULTS

Among 1000 infants, 766 were from Brazil and 234 were from South Africa, maintaining the same proportion of the parent cohort. Table 1 describes baseline characteristics of the women included in this analysis. Fifty percent of infants were female. The majority of mothers were of black or mixed black/white race, were an average of 26 years of age, had relatively high CD4 cell counts (median of 466 cells/mm^3) and had detectable viremia at the time of delivery. Ninety percent of women delivered infants at full term ($\geq$37 weeks), and mean infant birth weight was 3017 ± 518 g with approximately 7% of full-term infants being born small for gestational age. Mean infant birth weights were significantly lower in South Africa compared with that in Brazil. As with the primary

TABLE 1. Demographics, Clinical Parameters and Obstetric Parameters for Brazilian and South African Infants

	Total	South Africa	Brazil	*P* Value
Maternal race [n (%)]				<0.0001
White	208 (21.1)	0 (0.0)	208 (27.4)	
Black	480 (48.6)	222 (96.5)	258 (30.0)	
Brazilian native	9 (0.9)	0 (0.0)	9 (1.2)	
Mixed/Mulatto	283 (28.6)	0 (0.0)	283 (37.3)	
Other	8 (0.8)	8 (3.5)	0 (0.0)	
Maternal age (years)				0.0005
n	988	230	758	
Mean (std. dev.)	27.0 (6.2)	28.2 (6.0)	26.6 (6.2)	
Maternal CD4 count at entry (cells/mm^3)				0.7031
n	970	228	742	
Median (min–max)	466 (12–2556)	461 (41–2556)	468 (12–2160)	
Maternal viral load at entry (copies/mm^3)				0.5960
n	986	230	756	
Median (min–max)	13,580 (200–1,526,786)	13,030 (200–1,210,000)	14,084.5 (200–1,526,786)	
Mother received prenatal care?				<0.0001
Yes	660 (67.1)	84 (36.5)	576 (76.4)	
No	324 (32.9)	146 (63.5)	178 (23.6)	
Number of prenatal care visits				<0.0001
0	324 (33.2)	146 (64.3)	178 (23.7)	
1–2	161 (16.5)	36 (15.9)	125 (16.7)	
3+	492 (50.4)	45 (19.8)	447 (59.6)	
Birth weight (g)				<0.0001
n	1000	234	766	
Mean (SD)	3017.3 (517.9)	2855.7 (506.3)	3065.9 (512.8)	
Gestational age [n (%), wk]				0.0054
32–36	105 (10.5)	36 (15.4)	69 (9.0)	
≥37	895 (89.5)	198 (84.6)	697 (91.0)	

analysis, many women had received prenatal care but had not been identified and/or treated as HIV-infected.

Approximately 23% of all infants (n = 229) experienced ≥1 ISAE during the 6-month follow-up; 19% in South Africa (n = 44) and 24% in Brazil (n = 185). Figure 1 shows the frequency of ISAEs in the cohort. Adjusted per infant years (IY), the overall rate of ISAEs was 60/100 IY, with similar rates between Brazil and South Africa (61 vs. 59/100 IY) but varying by type of ISAE.

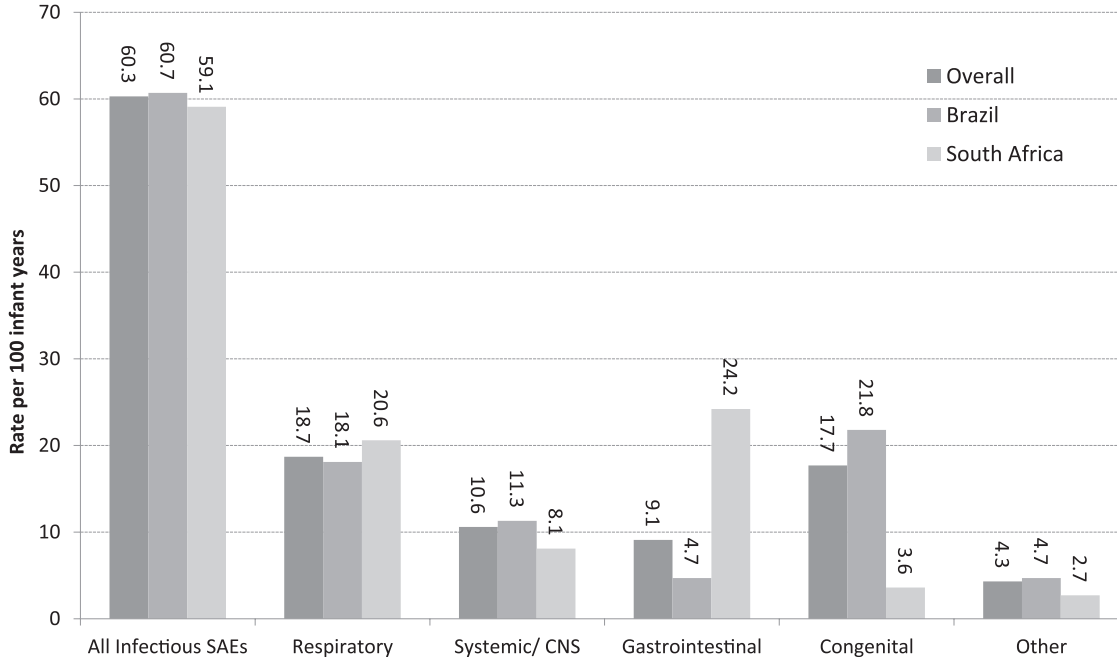

FIGURE 1. Infectious ISAEs among infants from Brazil and South Africa. Y-axis indicates rates of disease per 100 IY, and X-axis indicates infectious categories evaluated. Overall rates of ISAEs per 100 IY are in dark gray bars, Brazilian ISAE rates per 100 IY are in mid-gray bars and South African ISAE rates per 100 IY are in light gray bars as shown in legend. Gastrointestinal ISAEs were more common in South Africa, whereas congenital ISAEs were more frequently diagnosed in Brazil.

TABLE 2. Relationship of ISAEs With Infant and Maternal Characteristics

	(Infants With ≥1 ISAEs)/N (%)*	Brazil	South Africa	Both Sites		
		OR (95% CI)	OR (95% CI)	OR (95% CI)	AOR (95% CI)	*P* Value
Infant's characteristics						
Birth country						
Brazil	185/766 (24.2)			1		
South Africa	44/234 (18.8)			0.7 (0.5–1.1)		
Gestational age at delivery (wk)						
≥37	201/895 (22.5)	1	1	1		
32–36	28/105 (26.7)	1.2 (0.7–2.1)	1.6 (0.7–1.5)	1.3 (0.8–2)		
Maternal baseline characteristics						
Race						
White and others	41/216 (19)	1	1	1		
Black	100/480 (20.8)	1.4 (0.9–2.1)	0.4 (0.1–1.6)	1.1 (0.8–1.7)		
Brazilian native and mixed	85/292 (29.1)	1.8 (1.2–2.8)		1.8 (1.2–2.7)		
Years of education						
12+ yr	8/91 (8.8)	1	1	1	1	
9–11 yr	48/238 (20.2)	2.5 (0.7–8.8)	2.6 (0.9–7.2)	2.6 (1.2–5.8)	2.6 (1.2–5.9)	0.02
Completed 8 yr	29/117 (24.8)	2.7 (0.7–9.7)	5.6 (1.5–20)	3.4 (1.5–7.9)	3.5 (1.5–8.1)	0.004
<8 yr	140/541 (25.9)	3.1 (0.9–10.4)	4.8 (1.4–16)	3.6 (1.7–7.7)	3.7 (1.7–7.8)	0.001
Maternal characteristics						
Prenatal care?						
Yes	147/660 (22.3)	1	1	1		
No	76/324 (23.5)	1.3 (0.9–2)	0.9 (0.4–1.7)	1.1 (0.8–1.5)		
Log_{10} viral load, continuous viral load, copies/mL	225/986 (22.8)	1.1 (0.9–1.3)	1.1 (0.8–1.5)	1.1 (0.9–1.3)		
Undetectable	13/73 (17.8)	1	1	1	1	
<10,000	90/362 (24.9)	1.3 (0.6–2.6)	2.7 (0.6–12.6)	1.5 (0.8–2.9)	1.4 (0.7–2.7)	0.31
<10,001–100,000	91/437 (20.8)	0.95 (0.5–1.9)	2.6 (0.6–12)	1.2 (0.6–2.3)	1.1 (0.6–2.2)	0.71
100,001-1,000,000	27/108 (25)	1.5 (0.7–3.5)	1.8 (0.3–10)	1.5 (0.7–3.2)	1.4 (0.7–3.1)	0.34
>1,000,000	4/6 (66.7)	7.1 (0.6–86)	21 (1.3–346)	9.2 (1.5–56)	9.9 (1.6–63.1)	0.02
CD4 count (cells/mm^3)						
>500	91/438 (20.8)	1	1	1		
200–500	101/428 (23.6)	1.2 (0.8–1.7)	1.3 (0.6–2.7)	1.2 (0.9–1.6)		
<200	27/104 (26)	1.2 (0.7–2.1)	2.2 (0.8–6)	1.3 (0.8–2.2)		
Additional covariates						
WAZ at birth						
>−2 SD	193/886 (21.8)	1	1	1		
>3, ≤−2 SD	20/72 (27.8)	1.2 (0.6–2.4)	2 (0.8–5.2)	1.4 (0.8–2.4)		
≤−3 SD	16/42 (38.1)	2.9 (1.4–5.2)	1.6 (0.5–5.4)	2.2 (1.2–4.2)		
WAZ at 1 mo						
>−2 SD	167/810 (20.6)	1	1	1		
≤−2 SD, >−3	31/111 (27.9)	1.3 (0.8–2.2)	2.6 (1.1–6.4)	1.5 (1–2.3)		
≤−3 SD	25/62 (40.3)	2.7 (1.4–5.2)	3.1 (1.1–8.4)	2.6 (1.5–4.4)		
Illegal substances this pregnancy?						
No	202/901 (22.4)	1	1	1		
Yes	22/83 (26.5)	1 (0.6–1.8)		1.3 (0.8–2.1)		
Alcohol use this pregnancy?						
No (never)	140/630 (22.2)	1	1	1		
Yes	83/351 (23.7)	1 (0.8–1.7)	1.1 (0.5–2.5)	1.1 (0.8–1.5)		

*The numerator is the total number of infants who had at least 1 ISAE.

Gastrointestinal ISAEs were more common in South Africa with rates (95% CI) of 24.2/100 IY (15.1–33.3/100 IY) versus 4.7/100 IY in Brazil (2.5–6.9/100 IY), whereas congenital ISAEs were more frequently diagnosed in Brazil, 21.8/100 IY (17.1–26.5/100 IY) versus 3.6 100/IY (0.97–9.14/100 IY) in South Africa, primarily because of high congenital syphilis rates in Brazil.

Participating infants' vaccination status (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D175) shows that only 1.3% of infants in South Africa and 41% of infants in Brazil received immunization against rotavirus. Of note, rotavirus vaccine was unavailable during the majority of the study duration as it became available in Brazil in 2006 and in South Africa in 2009.[37] Furthermore, only 1.6% of infants in Brazil and none in South Africa received pneumococcal conjugate vaccine, which was made available in both countries in 2009.[37]

As seen in Table 2, the multivariate logistic regression model demonstrated that the probability of having at least 1 ISAE (grades 3–5) in formula-fed infants was associated with less than 12 years of maternal education compared with women with ≥12 years of education [adjusted odds ratio (AOR) (95% CI)): <8 years, 3.7 (1.7–7.8); 8 years, 3.5 (1.5–8.1); and 9–11 years, 2.6 (1.2–5.9)]. Similarly, having 1 ISAE was associated with maternal viral load at delivery of greater than 1,000,000 copies/mL compared with undetectable viral load (AOR, 9.9; 95% CI, 1.6–63.1). There were 101 instances of neutropenia recorded but only 6 patients with neutropenia probably or possibly secondary to zidovudine had an ISAE.

Undernutrition and stunting peaked at 1 month of age in both countries (Fig. 2). Both WAZ and HAZ improved by 6 months of age in Brazil ($P < 0.001$), but only WAZ improved statistically in South Africa by 6 months of age ($P < 0.001$ for WAZ; $P = 0.6$ for

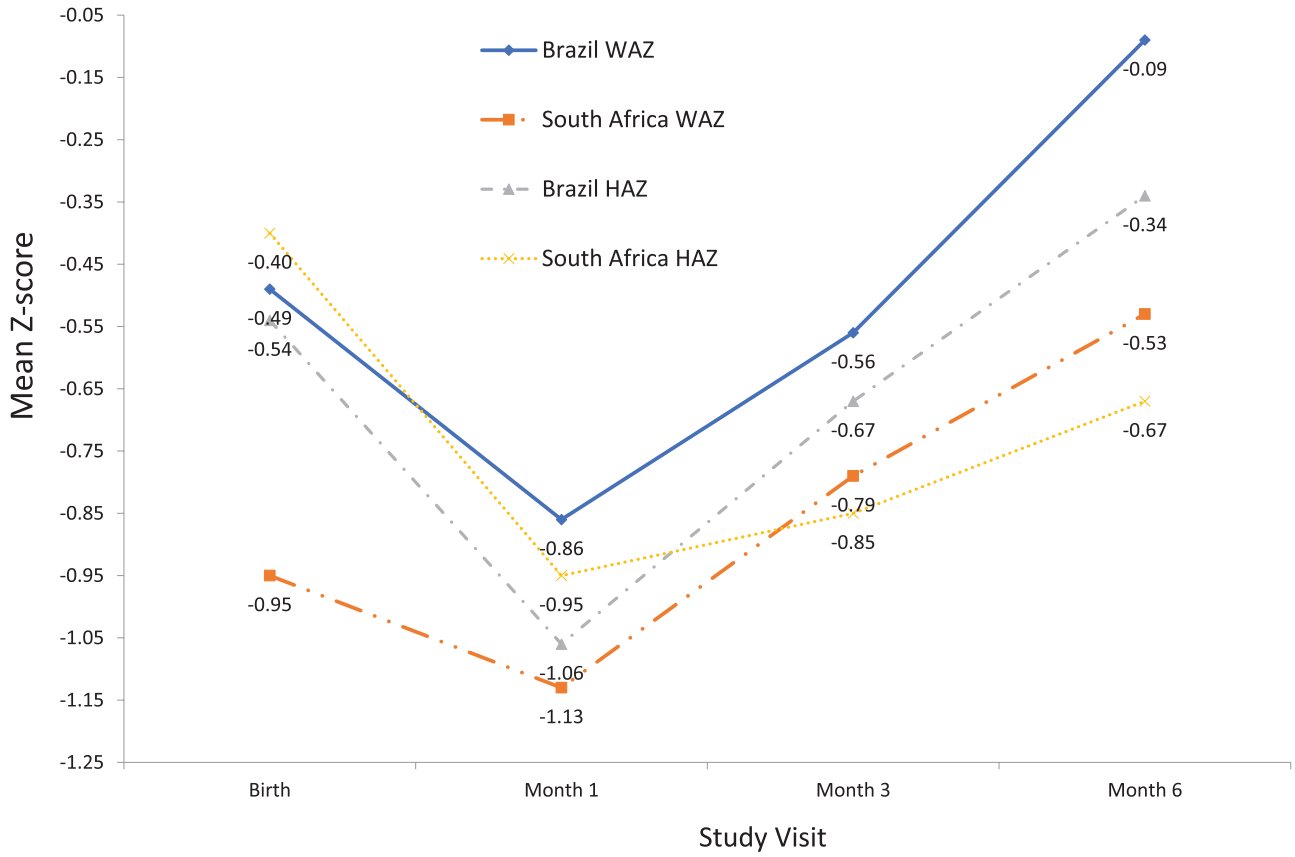

FIGURE 2. Height-for-age Z score (HAZ) and WAZ by study visit among 1000 infants from Brazil and South Africa. As seen, undernutrition and stunting peaked at 1 month and undernutrition improved by 6 months in both countries.

HAZ). At 1 month of age, 18% of all infants were undernourished (16% in Brazil and 23% in South Africa) and 22% were stunted (21% in Brazil and 25% in South Africa). At 3 months of age, 12% of all infants were undernourished (11% in Brazil and 16% in South Africa) and 18% were stunted (17% in Brazil and 24% in South Africa). At 6 months of age, 7.3% of all participants were undernourished (6.3% in Brazil and 11% in South Africa) and 14% were stunted (11% in Brazil and 26% in South Africa).

In Brazil, 7 (0.9%) infants died, and 15 infants (6.4%) died in South Africa (Table 3). Among deaths in Brazil, 4 infants died from pneumonia, and 3 succumbed to sepsis. The mean age of death was 114 days (range, 12–150 days) with an infant mortality rate (IMR, mean ± standard deviation) per 1000 of 9.1 ± 1.8 at 6 months of age. In South Africa, 4 infants died from pneumonia, 3 from gastroenteritis, 2 from sepsis, 5 from sudden infant death syndrome (as determined by site investigators) and 1 with congenital syphilis. The mean age of death in South Africa was 34.7 days (range, 1–196) with an IMR of 64.1 ± 3.0 at 6 months of age. In the final model, infant mortality was associated with South African birth (AOR, 6.2; 95% CI, 2.5–15.8); maternal viral load at delivery (AOR per 1 $\log_{10}$ increment: 1.7; 95% CI, 1.01–2.9); and low birth WAZ (birth WAZ ≤−2 to >−3: AOR, 5.2; 95% CI, 1.8–14.8 and birth WAZ ≤−3: AOR, 6.2; 95% CI, 1.8–21.3) compared with WAZ >−2. In the univariate analysis, gestational age <37 weeks, black race and lack of prenatal care were significantly associated with infant mortality but not in the final multivariable model. In the unadjusted model, cesarean section delivery was protective. As 93% of the cesarean sections were performed in Brazil, the lower infant mortality in Brazil likely confounded the univariate results.

DISCUSSION

In this population of formula-fed HEU infants born to mothers who did not receive ART before labor and delivery, there were high rates of syphilis, cytomegalovirus, gonorrhea and chlamydia coinfections in both mothers and infants in this cohort.[38–40] In addition, given the growing evidence that HEU infants may be more vulnerable to infections and mortality compared with the general population, especially in the absence of breast-feeding, high rates of adverse events in the cohort were anticipated.

The high rates of undernutrition and stunting in our formula-fed cohort are consistent with results of prior studies.[41] In Brazil, WHO reported that 5.1% of all infants in the general population between 0 and 6 months of age suffered undernutrition between 2006 and 2007, a lower proportion than the 6.3% observed in our vulnerable HEU cohort.[42] However, in South Africa, WHO reported that 15.8% of infants 0 and 6 months were undernourished between 2003 and 2005,[43,44] which is significantly higher than the 11% observed in this cohort. Of note, we used the WHO growth charts for our measurements as they are accepted as the standard guide in both Brazil and South Africa, which were developed by measuring breast-feeding infants. Given that formula-fed infants tend to gain weight faster during infancy compared with breast-fed infants,[45] there may be some underestimation of the level of undernutrition in our formula-fed population.

We noted that rates of stunting and undernutrition peaked at 1 month of life and improved by 6 months of life. It is unknown whether in utero exposure to HIV or exposure to antiretrovirals during the first few weeks of life contributed to these high rates of undernutrition and stunting. Nevirapine-based regimens have

TABLE 3. Relationship of Infant Mortality With Maternal Characteristics and Undernutrition Status

	Death/N (%)	Brazil	South Africa	Both Sites		
		OR (95% CI)	OR (95% CI)	OR (95% CI)	AOR (95% CI)	*P* Value
Infant's characteristics						
Birth country						
Brazil	7/766 (0.91)			1	1	
South Africa	15/234 (6.4)			7.4 (3–19)	6.22 (2.5–16)	<0.001
Gestational age at delivery (wk)						
≥37	15/895 (1.7)	1	1	1		
32–36	7/105 (6.7)	1.69 (0.2–14.3)	4.2 (1.4–4.6)	4.2 (1.7–10.5)		
Maternal baseline characteristics						
Age (yr)						
≤24	10/380 (2.6)	1.5 (0.25–INF)	1.5 (0.5–4.6)	1.2 (0.5–3)		
25–34	10/467 (2.1)	1	1	1		
≥35	2/141 (1.4)		0.8 (0.2–4)	0.7 (0.1–3)		
Race						
White and others	0/216 (0)	1	1			
Black	16/480 (3.3)	0.81 (0.02–INF)	0.8 (0.11–INF)	1.6 (0.6–4.3)		
Brazilian native and mixed/Mulatto	6/292 (2.1)	5.9 (0.9–INF)		1		
Years of education						
12+ yr	2/91 (2.2)	1	1	1		
9–11 yr	8/238 (3.4)		2.2 (0.4–10.4)	1.6 (0.3–7.4)		
Completed 8 yr	3/117 (2.6)	0.3 (0.01–INF)	3.1 (0.4–23.6)	1.2 (0.2–7.2)		
<8 yr	9/541 (1.7)	0.5 (0.07–INF)	3.3 (0.5–20.8)	0.8 (0.2–3.5)		
Maternal characteristics at delivery						
Prenatal care during pregnancy?						
Yes	8/660 (1.2)	1	1	1		
No	14/324 (4.3)	1.3 (0.3–6.8)	2.4 (0.7–8.8)	3.7 (1.5–8.9)		
Mode of delivery						
Vaginal	20/605 (3.3)	1	1	1		
Cesarean section	2/382 (0.5)	0.2 (0.02–1.6)	0.5 (0.06–3.9)	0.2 (0.04–0.7)		
Viral load (log_{10} copies/mL)	22/986 (2.2)	2.9 (1.03–8.3)	1.5 (0.8–2.6)	1.9 (1.1–3.3)	1.7 (1.01–2.9)	0.048
Viral load (copies/mL)						
Undetectable	1/73 (1.4)	1	1	1		
<10,000	4/362 (1.1)		1.2 (0.1–11)	0.8 (0.1–7.3)		
10,001–100,000	13/437 (3)	1.19 (0.17–INF)	1.8 (0.2–15)	2.2 (0.3–17)		
100,001-1,000,000	3/108 (2.8)	0.68 (0.02–INF)	1.4(0.1–16)	2.1 (0.2–20)		
>1,000,000	1/6 (16.7)		11 (0.5–250)	14.4 (0.8–266)		
CD4 count (cells/mm^3)						
>500	7/438 (1.6)	1	1	1		
200–500	11/428 (2.6)	2.1 (0.4–11.6)	1.33 (0.4–4.3)	1.6 (0.6–4.2)		
<200	4/104 (3.9)	2.2 (0.2–24)	2.5 (0.6–11)	2.5 (0.7–8.6)		
Additional covariates						
WAZ at birth >−2	12/876 (1.4)	1	1	1	1.00	
WAZ at birth ≤−2, >−3	6/71 (8.5)	2.9 (0.3–26)	7 (2–24.3)	6.7 (2.4–18.3)	5.2 (1.8–14.8)	0.002
WAZ at birth ≤−3	4/41 (9.8)	5.5 (0.6–49)	6.2 (1.4–26.7)	7.8 (2.4–25.3)	6.2 (1.8–21.3)	0.004
Illegal substances in pregnancy?						
No	21/901 (2.3)	1	1	1		
Yes	1/83 (1.2)		15 (0.9–258)	0.5 (0.07–3.9)		
Alcohol use this pregnancy?						
No(never)	15/630 (2.4)	1.00	1.00	1		
Yes	7/351 (2)	0.6 (0.1–3)	2.2 (0.7–6.8)	0.8 (0.3–2.1)		

INF indicates infinity.

been associated with improved growth in infants with HIV infection.[46] Our analyses did not support differing rates of undernutrition with any of the infant prophylaxis regimens, but we were using short courses of nevirapine and nelfinavir as prophylaxis regimens in HEU infants and not as treatment. Furthermore, infants in our study did not have antenatal exposure to antiretroviral drugs. With 53%–55% of all childhood deaths attributable to undernutrition,[47–49] optimizing the nutritional status of HEU infants should be an area of intense evaluation.

Although rare, viral loads greater than 1 million copies/mL were associated with increased rates of infectious serious adverse events, supporting an association between maternal viral load and infections in HEU infants as reported by other investigators from South Africa, Zambia and Kenya.[18,28,50–52] Maternal viral load could potentiate dysregulation of an infant's immune system, as higher maternal viral loads have been associated with decreased maternal antibody transfer during the third trimester, decreased number of circulating T cells and impaired T-cell maturation in HEU infants.[53,54] In addition, the immunologic properties of breast milk may vary considerably between women with immune reconstitution after antiretroviral treatment versus those with advanced HIV disease.[55,56] Furthermore, HIV-infected mothers with high-level viremia may be more physically affected by disease and less able to provide appropriate childcare to their infants compared with healthy mothers. As maternal viral load is a known major predictor of perinatal HIV transmission,[57] every effort must be taken to suppress viremia as quickly and as early as possible in HIV-infected women to promote maternal health, to reduce transmission and to potentially reduce morbidity and mortality in HEU infants. Evidence has been inconclusive as to whether the higher susceptibility

to infections in HEU infants is because of potential HIV exposure in utero or antiretroviral drug exposure during pregnancy and breast-feeding.[58,59] Our study supports the hypothesis that increased morbidity and mortality in HEU infants may be potentially caused by exposure to maternal HIV because infants in this study were not exposed to antiretroviral drugs in utero or through breast milk.

In general, rates of ISAEs in our cohort were similar or lower than those reported in other studies looking at hospitalizations, infectious pneumonia and gastroenteritis in formula-fed HEU infants in Brazil and South Africa.[28,50] When comparing rates of ISAE (focused on gastroenteritis and lower respiratory tract infection) as described by the Kesho Bora study which included sites in South Africa, our rate of 44.8/100 IY was similar to their rate of 47.2/100 IY in the "never breast-feeding group," but notably higher than the rates of 10.9/100 IY reported in the exclusively breast-fed population.[10] Similarly, our calculated IMR of 64.1/1000 live births in the South African infants is similar to IMR reported by other studies performed in South Africa with formula-fed infants, but higher than the IMR reported in South African breast-fed infants of 35–51/1000 live births[28,51] and higher than IMR for South Africa as reported by United Nations Children's Fund (52.8/1000 live births in 2004 decreased to 37.1/1000 live births in 2011).[60] Our calculated IMR of 9.1/1000 in Brazil was lower than general population IMRs reported for Brazil (21/1000 live births in 2004 decreased to 14.4/1000 live births in 2011).[60]

Both Brazil and South Africa are upper middle-income countries with growing populations of HEU infants. While our study provides evidence for possible contributors to morbidity and mortality in this population, it has weaknesses. First, this was a clinical research study with close medical follow-up of patients, which may limit the generalizability of results. Second, we did not have a control arm of HEU breast-fed infants because the parent study excluded breast-feeding infants. However, we were able to compare our data with other studies done in similar populations. At the time of this study, formula-feeding was an acceptable option for HIV-infected women in South Africa, and thus, our study is unique in being able to collect and analyze extensive information on infant outcomes for a very large cohort of formula-fed HEU infants with very close follow-up. Our findings support the WHO recommendations and the South African 2015 National Consolidated Guidelines for PMTCT, promoting breast-feeding as an important option for HIV-infected African women who are on appropriate ART as breast-feeding appears to decrease incidence of infectious morbidity and mortality.[32,61,62]

CONCLUSIONS

In conclusion, birth WAZ scores and high maternal HIV viral load were significantly associated with infant morbidity and mortality in formula-fed HEU infants. Given high rates of diarrhea and pneumonia reported in this population, prompt and complete vaccination against rotavirus and pneumococcal infections in these high-risk infants is of paramount importance. Addressing these modifiable risk factors could improve morbidity and mortality in infants born to HIV-infected women.

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