Brief Report

HIV-Exposed Uninfected Infants are at Increased Risk for Severe Infections in the First Year of Life

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Summary

HIV-exposed uninfected (HEU) infants have higher infectious morbidity than HIV-unexposed uninfected (HUU) infants. We present the clinical outcomes from a pilot cohort study of 27 HEU and 28 HUU infants. In the absence of infant malnutrition or advanced maternal HIV, HEU infants experienced a 2.74 (0.85–8.78) times greater risk of hospitalization in the first year.

Key words: HIV-exposed infants, HIV, vertical transmission prevention, PMTCT, South Africa.

Introduction

South Africa's (SA) antenatal HIV seroprevalence is 30% [1] with perinatal HIV infection reduced to <5% by vertical transmission prevention (VTP) [2]. More than a quarter of SA's newborns are HIV exposed but uninfected (HEU) and may have increased mortality and morbidity compared to infants born to HIV-uninfected mothers [3, 4]. Avoidance of breastfeeding is catastrophic in areas with high infectious disease burdens and malnutrition [5, 6]. But it is not only formula-fed HEU infants that experience more frequent infections and death [4, 7], the reasons for this being multi-factorial [5, 8, 9]. This report compares infection-related outcomes of HEU and HIV-unexposed uninfected (HUU) infants in the first year of life.

During this study, VTP prophylaxis in SA consisted of maternal and infant short-course zidovudine with single-dose nevirapine. Maternal CD4 count <200 cells μl^{-1} qualified for lifelong combination

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antiretroviral therapy (cART). The program provided 6 months of infant formula for mothers choosing not to breastfeed.

Methods

In 2009, a pilot cohort of HEU and HUU infants were recruited at birth and assessed at 2, 6, 12, 24 and 52 weeks for clinical outcomes. All infants were confirmed as HIV uninfected by HIV-DNA-PCR at 2, 6 and 12 weeks. Maternal demographic, obstetric and social characteristics were collected. HIV-uninfected mothers' HIV-infection status was serologically confirmed [10]. Unblinded medical professionals conducted the infant health history and examination. The primary clinical outcome was infection-associated hospitalizations, extracted from the hospital chart after caregiver self-report. Hospitalizations were graded for severity from 1 (mild) to 5 (fatal) according to the Division of Aids (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [11]. Anthropometry was compared as WHO *Z*-scores. The relative risk (RR) for infection-associated hospitalization was calculated comparing the number of infants hospitalized at least once in each group. Both, a cumulative incidence ratio, including only infants with complete follow-up to 12 months, as well as an incidence rate ratio, including all infants with any duration of follow-up with the denominator as number of months of follow-up, were calculated. Two-sided α was set at 0.05 and Bonferroni adjustment for multiple comparisons was applied. Statistical analysis was performed using R version 2.13.1.

TABLE 1
Maternal and infant characteristics

	Total (55)	HEU (27)	HUU (28)	*p*-value
Maternal characteristics				
Age (in years)—mean (SD)	26.6 (6.3)	25.9 (6.8)	27.3 (5.7)	0.4
Multigravida (%)	40 (73)	21 (78)	19 (68)	0.6
Received antenatal care (%)	48 (87)	24 (89)	24 (86)	1
Completed secondary education (%)	15 (27)	6 (22)	9 (32)	0.6
Smoked during pregnancy (%)	14 (25)	3 (11)	11 (39)	0.17*
Consumed alcohol during pregnancy (%)	4 (7)	0 (0)	4 (14)	0.11
HIV diagnosed during pregnancy (%)		14 (52)		
Antenatal CD4 count in cells μl^{-1}—median (range)		337 (131–673)		
Antiretroviral exposure				
None (%)		3 (11)		
cART (%)		4 (15)		
VTP prophylaxis (%)		19 (70)		
Unknown		1 (4)		
Infant characteristics				
Male (%)	22 (40)	7 (26)	15 (54)	0.35*
Ethnicity				0.001*
African[a] (%)	30 (55)	22 (81)	8 (29)	
Mixed or Caucasian[b] (%)	25 (45)	5 (19)	20 (71)	
Birthweight—mean (95% CI) (g)	2966 (2857–3075)	2945 (2866–3024)	2986 (2830–3142)	0.7
Gestational age in weeks—mean (95% CI)	37.8 (37.1–38.4)	37.7 (36.7–38.7)	37.9 (37.0–38.7)	0.8
Received any breastfeeding (%)	29 (53)	1 (4)	28 (100)	<0.001*
Infant anthropometry				
6 months—*n*	47	25	22	
WAZ (SD)	–0.25 (1.07)	+0.17 (0.95)	–0.73 (1.16)	0.03*
LAZ (SD)	–0.64 (1.26)	–0.44 (1.05)	–0.87 (1.61)	0.42
WLZ (SD)	+0.32 (1.16)	+0.68 (1.05)	–0.09 (1.17)	0.13*
12 months—*n*	44	23	21	
WAZ (SD)	–0.09 (1.16)	+0.26 (1.13)	–0.47 (1.09)	0.18*
LAZ (SD)	–0.20 (1.29)	+0.10 (1.09)	–0.53 (1.43)	0.22
WLZ (SD)	+0.04 (1.15)	+0.32 (1.05)	–0.26 (1.19)	0.10

[a]African includes infants of Xhosa speaking South African ($n = 27$), Malawian ($n = 2$) and Zimbabwean ($n = 1$) descent
[b]All mixed ethnicity except 1 Caucasian HUU
*Adjusted for multiple comparisons.
SD, standard deviation; WAZ, weight-for-age *Z*-score; LAZ, length-for-age *Z*-score.

Results

Fifty-five infants were enrolled at 2 weeks of age, 27 HEU and 28 HUU. All HEU infants remained HIV uninfected at 6 and 12 weeks in the absence of breastfeeding. Maternal and infant characteristics are shown in Table 1. The median duration of exclusive breastfeeding in HUU infants was 12 weeks. Three infants, 2 HUU at 6 months and 1 HEU at 12 months had moderate acute malnutrition with a weight-for-length *Z*-score (WLZ) less than −2.

There was no difference in the number of caregiver-reported infectious events; 14.7 (11.4–18.9) compared to 13.9 (10.7–18.1) events per 100 months of infant follow-up in HEU and HUU infants, respectively. Fourteen infants were hospitalized at least once: 14 hospitalizations in 10 HEU infants and 4 hospitalizations in 4 HUU infants. Nine of 14 (64%) HEU and 3 of 4 (75%) HUU hospitalizations occurred during the first 6 months. Among infants who completed follow-up to 12 months (23 HEU and 21 HUU), the RR for hospitalization was 2.74 (0.85–8.78) times greater for HEU than HUU. HEU infants experienced an incidence rate of 3.4 (1.86–6.26) hospitalized infants per 100 infant-months, compared to 1.4 (0.57–3.60) in HUU infants for an RR of 2.42 (0.70–10.59).

Lower respiratory infections accounted for 50% (9/18) of the hospitalizations. The remaining events were severe gastroenteritis (3 HEU), culture confirmed urinary tract infections (2 HEU and 1 HUU), neonatal sepsis (1 HUU), varicella zoster (1 HEU) and measles (1 HEU). The median DAIDS grade was 3 in each group. One HUU and two HEU infants were hospitalized for events graded <3. One grade 4 event occurred in an HEU infant and one grade 5 (fatal) adenovirus pneumonia in an HUU infant at 8 months.

All 14 hospitalized infants were appropriately immunized, were not severely anemic and had 6-month WLZ above the mean for the cohort. Three fully immunized HEU infants with normal growth and born to mothers with CD4 counts >350 cells μl^{-1} each experienced ≥2 hospitalizations.

Discussion

Twice as many HEU infants had at least one infection-associated hospitalization in the first year of life. This difference was not statistically significant, possibly due to inadequate power of the small sample. This suggests though that HEU infants are not experiencing a greater number of infectious events but are at higher risk for more severe events requiring hospitalization. Low birthweight, prematurity, missed immunizations, malnutrition, infant anemia and severe maternal immunosuppression did not account for the infectious morbidity in this cohort. Comparison by feeding mode was not possible with only one breastfed HEU infant. However, HEU infants were not compromised nutritionally as measured by anthropometry and the majority of severe infections were respiratory, not gastrointestinal. In early infancy, breastfeeding protection against diarrhea is substantially greater than protection against respiratory infections [12] suggesting that this cohort was not particularly disadvantaged due to absence of breastfeeding alone.

Admitting clinicians were not blinded to HIV-exposure status and hospitalization bias was considered. However, the DAIDS grade of hospitalization events ≥3 (75% HUU and 80% HEU), suggests limited if not absent indication bias. Detailed socioeconomic data were not available to determine the role of poverty, social, parenting and household circumstances, but these are important considerations. The entire cohort accessed free government health services and maternal education was similar, diminishing the likelihood of gross differences in socioeconomic position and quality of health care. A gradient of HEU risk determined largely, but not exclusively, by feeding practice and maternal HIV disease severity exists [8]. This risk has not been well quantified against HUU infants and although small, the strength of this cohort is the direct comparison of HEU to HUU infants.

In this cohort, HEU infants experienced increased infection-related hospitalizations in the first year of life in the absence of an increased number of infectious events, advanced maternal HIV disease or infant malnutrition. As even breastfed HEU infants experience greater infectious morbidity and mortality than HUU infants [4, 7] prospective consideration of other maternal, environmental and infant host risk factors is required.

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