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Journal of the Pediatric Infectious Diseases Society

BRIEF REPORT

Association of HIV Exposure and HIV Infection With In-hospital Mortality Among Hospitalized Infants <1 Year of Age, South Africa, 2016–2018

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We enrolled 1323 hospitalized infants aged <1 year in 2016–2018, and examined the association between HIV status and in-hospital mortality. After controlling for confounders, HIV-exposed uninfected infants did not have an increased risk of mortality, whereas infants living with HIV had 4 times greater risk compared with HIV-uninfected infants.

Key words. Africa; HIV exposure; HIV infection; infants; mortality.

INTRODUCTION

While infants living with HIV (HI) are known to be at increased risk of mortality compared with HIV unexposed uninfected (HUU) infants [1], the effect of HIV exposure on infant mortality is less well understood with much of the data from prior to widespread antiretroviral therapy (ART) use, and from non-African countries [2].

In a national antenatal survey in 2017, 31% of pregnant women in South Africa were living with HIV [3]. A national program for prevention of vertical transmission of HIV was implemented in 2002 and was expanded and improved over time so that from 2015 all women living with HIV were eligible for lifelong ART, irrespective of CD4 count, as well as the availability of combination therapy [4]. This program has successfully reduced the risk of vertical HIV transmission; however, there is a growing population of HIV-exposed uninfected (HEU) infants. In a meta-analysis in 2016 of 22 studies conducted between 1986 and 2013, the pooled estimate showed that HEU infants had more than a 70% increased risk of all-cause mortality compared with HUU infants within the first 2 years of life, although there was heterogeneity between the individual studies [5].

We aimed to determine whether HIV exposure and HIV infection were associated with an increased risk of in-hospital mortality among infants hospitalized with acute medical illness, in the context of an established ART program.

METHODS

The Infant Burden Study was conducted to assess the burden of disease associated with influenza and other respiratory pathogens among hospitalized infants at 3 sentinel surveillance hospitals located in 3 (KwaZulu-Natal, Mpumalanga, and North West) provinces from July 2016 through October 2018. Surveillance officers enrolled infants aged <1 year admitted to the medical ward with acute (symptom onset ≤10 days) respiratory and non-respiratory medical illness (excluding trauma/surgical cases), including medical admissions to the ICU. Surveillance officers collected whole blood, and demographic and clinical information by structured interview with parent/caregiver and hospital record review. Infants were followed up until discharge or in-hospital death.

Infant HIV status was determined from standard of care testing during the admission, or through testing at enrollment by polymerase chain reaction (PCR). HUU infants were infants with a negative HIV result and a recently documented (<3 months) negative maternal HIV status. HEU infants were infants with a negative HIV result and a recently documented or verbally reported positive maternal HIV status, evidence that the mother was taking ART during pregnancy or postpartum. HI infants were infants with a recently documented positive HIV result, verbally reported by the parent/caregiver, or evidence that the infant was receiving ART. If the mother's HIV status was unknown or a negative test result was from >3 months prior, the mother was offered voluntary counseling and testing.

A cross-sectional analysis was conducted to assess the association between infant HIV status and in-hospital mortality. Factors associated with mortality were assessed using univariate random effects logistic regression, accounting for clustering

Received 1 August 2023; editorial decision 6 November 2023; accepted 10 November 2023
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Journal of the Pediatric Infectious Diseases Society 2023;12(12):646–651
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https://doi.org/10.1093/jpids/piad100

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by site. Potential confounders ($P < .2$) from this analysis were examined individually for their effect on the association between HIV status and mortality, with evidence of confounding considered if the main effect adjusted odds ratio (aOR) differed by >10% from the unadjusted odds ratio (OR) for either HI or HEU compared with HUU infants. Length of hospital stay, oxygen therapy, and intensive care unit admission were considered to be on the causal pathway, and not assessed for confounding. Multivariable random effects logistic regression accounting for clustering by site was performed, adjusting for the identified confounders. *A priori* variables included age, vaccination status, and feeding type.

Sensitivity analyses of the final model was performed by (1) comparing the risk of in-hospital mortality in HI compared with HIV-uninfected (grouping together both HUU and HEU) infants, and (2) restricting the analysis to infants aged <6 months. Statistical analyses were performed using Stata version 14.0.

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (M140824) and University of KwaZulu-Natal Biomedical Research Ethics Committee (BE605/16). This surveillance was deemed nonresearch by the US Centers for Disease Control and Prevention.

RESULTS

During the study period, 1323 infants were enrolled, of which 1321 (99.8%) had known in-hospital outcome and 1296 (98.0%) had known HIV status. The most common admission diagnoses were pneumonia (538/1314, 40.9%) and diarrhea (191/1314, 14.5%), with 52.0% (683/1314) admitted with a respiratory diagnosis (Supplementary Table 1). Two percent (27/1321) of infants died while in hospital.

Overall, 55.8% (723/1296) of infants were HUU, 40.6% (526/1296) were HEU, and 3.6% (47/1296) were HI. Characteristics of enrolled infants by HIV status are shown in Table 1. The mortality ratio was 1.7% (12/721), 1.5% (8/526), and 12.8% (6/47) among HUU, HEU, and HI infants, respectively.

Among the 38/47 (80.9%) HI infants with information available, 92.1% (35/38) had mother's that received ART during pregnancy. For 28 HI infants with available information, 21 (75.0%) were receiving ART at the time of admission. Of 523 HEU infants with available data, 513 (98.1%) had mother's that were receiving ART during pregnancy.

The OR for mortality for HEU infants was 0.99 (95% confidence interval (CI) 0.40–2.44) and for HI infants was 7.39 (95% CI 2.58–21.19), compared with HUU infants (Table 2). Infant mortality by demographic and clinical characteristics, stratified by HIV status, is shown in Supplementary Table 2. After adjusting for a priori confounders, as well as the identified confounders (malnutrition and maternal education, Supplementary Table 3), HEU infants were not at increased risk of mortality compared with HUU (aOR 0.80, 95% CI .31–2.09), whereas HI infants had over 4 times increased risk of death compared with HUU (aOR 4.79, 95% CI 1.49–15.37) (Table 2). Malnutrition and not being fully vaccinated were also associated with an increased risk of mortality.

HI infants remained at increased risk of mortality compared with all HIV-uninfected (HUU and HEU) infants (Supplementary Table 4). When restricting to infants aged <6 months, HI but not HEU, were at increased risk of mortality compared with HUU infants (Supplementary Table 5).

DISCUSSION

In the context of a mature program for prevention of vertical HIV transmission this study found that HI infants, but not HEU infants, were at increased risk of in-hospital mortality compared with HUU infants. Malnutrition and not being fully vaccinated for age were also identified as risk factors for in-hospital mortality.

The proportion of infants that were HEU and HI were higher than was expected based on the reported HIV prevalence (31%) of women who attended antenatal care in 2017 [3], as well as that reported in a cross-sectional survey conducted in 2012–2013 (33.1% HEU and 2.6% HI) [6]. This may be due to these studies having been conducted among pregnant women and infants presenting for routine immunization, whereas our study was conducted among admitted infants, with HEU and HI infants more likely to be hospitalized [7].

Previous studies examining the association between HIV exposure and mortality have reported conflicting results. In a study conducted in 2010–2013 among infants aged <6 months hospitalized with lower respiratory tract infection in South Africa, HEU infants had 2.1-times increased risk of mortality compared with HUU infants [8], although feeding type was not adjusted for. In another study, among infants aged <6 months in South Africa in 2012–2013, the risk of hospitalization or death was 4-fold higher among HEU infants compared with HUU [9], although the CI included 1. A more recent study in a South African cohort of infants <1 year in 2017–2019 showed that while infectious-cause hospitalization was higher for HEU than HUU infants, there was no difference in mortality [10]. Data from the Thembisa model showed that ART coverage among adult females in 2018 in South Africa was 63% [11]. Use of ART in the mothers of HEU infants, and thereby improved health and well-being of the mother during and after pregnancy, would have likely resulted in transfer of protective maternal antibodies as well as improved infant care and nutrition.

Malnutrition was identified as a risk factor for mortality, with an increased mortality ratio in HUU, HEU, and HI infants compared with well-nourished infants with the same HIV status. Similarly, in the CHAMPS study in 7 countries in 2016–2020,

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Table 1. Characteristics of Infants <1 Year of Age Enrolled in the Infant Burden Study, Overall and by HIV Status, South Africa, July 2016–October 2018 (*N* = 1323)

Variable	Categories	No. (%) *N* = 1323	HIV Unexposed Uninfected (HUU) No. (%) *N* = 723	HIV-exposed Uninfected (HEU) No. (%) *N* = 526	HEU vs HUU *P*-value[g]	Living with HIV (HI) No. (%) *N* = 47	HI vs. HUU *P*-value[g]
Site	Mpumalanga	214 (16.2)	114 (15.8)	73 (13.9)	.075	16 (34.0)	.001
	KwaZulu-Natal	683 (51.6)	364 (50.4)	299 (56.8)		12 (25.5)	
	North West	426 (32.2)	245 (33.9)	154 (29.3)		19 (40.4)	
Year	2016	177 (13.4)	105 (14.5)	62 (11.8)	.369	8 (17.0)	.493
	2017	575 (43.5)	308 (42.6)	229 (43.5)		23 (49.0)	
	2018	571 (43.2)	310 (42.9)	235 (44.7)		16 (34.0)	
Sex	Male	763 (57.7)	415 (57.4)	305 (58.0)	.836	26 (55.3)	.780
	Female	560 (42.3)	308 (42.6)	221 (42.0)		21 (44.7)	
Race	Black	1303 (98.5)	706 (97.7)	523 (99.4)	.013	47 (100.0)	.288
	Non-black	20 (1.5)	17 (2.3)	3 (0.6)		0 (0.0)	
Age group (months)	<1	108 (8.2)	56 (7.8)	51 (9.7)	.344	1 (2.1)	.177
	1 to <3	364 (27.5)	207 (28.6)	137 (26.1)		10 (21.3)	
	3 to <6	335 (25.3)	188 (26.0)	120 (22.8)		15 (31.9)	
	6 to <9	277 (20.9)	148 (20.5)	118 (22.4)		8 (17.0)	
	9 to <12	239 (18.1)	124 (17.2)	100 (19.0)		13 (27.7)	
Underlying condition[a]	No	1284 (97.0)	698 (96.5)	513 (97.5)	.316	46 (97.9)	.625
	Yes	39 (3.0)	25 (3.5)	13 (2.5)		1 (2.1)	
Malnutrition[b]	No	975 (73.7)	556 (76.9)	382 (72.6)	.145	21 (44.7)	<.001
	Yes	347 (26.2)	166 (23.0)	144 (27.4)		26 (55.3)	
	Unknown	1 (0.1)	1 (0.1)	0 (0.0)		0 (0.0)	
Feeding type	Exclusive breastfeeding	707 (53.4)	427 (59.1)	248 (47.2)	<.001	21 (44.7)	.066
	Mixed feeding	240 (18.1)	142 (19.6)	82 (15.6)		12 (25.5)	
	Formula feeding	333 (25.2)	130 (18.0)	182 (34.6)		14 (29.8)	
	Unknown	43 (3.3)	24 (3.3)	14 (2.7)		0 (0.0)	
Prematurity[c]	No	1082 (81.8)	585 (80.9)	428 (81.4)	.839	42 (89.4)	.149
	Yes	241 (18.2)	138 (19.1)	98 (18.6)		5 (10.6)	
Birthweight[d]	Normal	970 (73.3)	533 (73.7)	384 (73.0)	.516	32 (68.1)	.003
	Low	282 (21.3)	153 (21.2)	121 (23.0)		7 (14.9)	
	Unknown	71 (5.4)	37 (5.1)	21 (4.0)		8 (17.0)	
Vaccination[e]	Full coverage	964 (72.9)	530 (73.3)	378 (71.9)	.646	37 (78.7)	.013
	No full coverage	307 (23.2)	167 (23.1)	132 (25.1)		5 (10.6)	
	Unknown	52 (3.9)	26 (3.6)	16 (3.0)		5 (10.6)	
Admission diagnosis[f]	Non-respiratory	631 (47.7)	320 (44.3)	283 (53.8)	.003	17 (36.2)	.470
	Respiratory	683 (51.6)	399 (55.2)	239 (45.4)		30 (63.8)	
	Unknown	9 (0.7)	4 (0.6)	4 (0.8)		0 (0.0)	
Maternal education level	None/Primary	616 (46.6)	300 (41.5)	268 (51.0)	.004	33 (70.2)	.001
	Secondary/Tertiary	694 (52.5)	414 (57.3)	254 (48.3)		14 (29.8)	
	Unknown	13 (1.0)	9 (1.2)	4 (0.8)		0 (0.0)	
Outcome	Survived	1294 (97.8)	709 (98.1)	518 (98.5)	.473	41 (87.2)	<.001
	Died	27 (2.0)	12 (1.7)	8 (1.5)		6 (12.8)	
	Unknown	2 (0.2)	2 (0.3)	0 (0.0)		0 (0.0)	

[a]Underlying condition includes asthma, chronic lung, heart, liver or renal disease, stroke, sinusitis, organ transplant, anemia, immunosuppressive therapy, splenectomy, diabetes, burns, immunoglobulin deficiency, autoimmune disease, nephrotic syndrome, cancer, spinal cord injury, seizure disorder, cerebral palsy, congenital heart disease, other congenital disorder, obesity, or chronic gastrointestinal problems.

[b]Malnutrition defined as a weight-for-age <−2 standard deviations from the WHO mean *Z*-score.

[c]Prematurity defined as gestational age at birth of <37 weeks.

[d]Low infant birthweight defined as <2500 g.

[e]Vaccination defined as full vaccine coverage for age, using the *Haemophilus influenzae* type b vaccine given as part of the routine infant immunization schedule at 6,10, 14 weeks as a proxy.

[f]Admission diagnosis: respiratory diagnosis includes apnea, neonatal sepsis, bronchiolitis, pneumonia, tuberculosis, and bronchitis and non-respiratory diagnosis includes encephalitis, viral illness, diarrhea, febrile seizures, meningitis, sepsis (non-neonatal), and other diagnosis.

[g]Chi-squared test calculated for known data (unknown excluded).

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Table 2. Demographic and Clinical Factors Associated With In-hospital Mortality Among Infants Aged <1 Year, South Africa, July 2016–October 2018

Variable	Categories	Total, No. *N* = 1321	No. of deaths *N* = 27	Mortality ratio, % (95% CI)	*P*-value [g]	Odds ratio[h] (95% CI)	*P*-value	Adjusted OR[i] (95% CI)	*P*-value
HIV status	HUU	721	12	1.7 (0.9–2.9)	<.001	Reference		Reference	
	HEU	526	8	1.5 (0.7–2.3)		0.99 (0.40–2.44)	0.974	0.80 (0.31–2.09)	.652
	HI	47	6	12.8 (4.7–27.8)		7.39 (2.58–21.19)	<0.001	4.79 (1.49–15.37)	.008
	Unknown	27	1	3.7 (0.1–19.0)		2.06 (0.25–16.83)	0.499	1.94 (0.21–17.91)	.557
Site	Mpumalanga	214	6	2.8 (1.0–6.1)	<.001	N/A			
	KwaZulu-Natal	682	4	0.6 (0.2–1.5)		N/A			
	North West	425	17	4.0 (2.3–6.4)		N/A			
Year	2016	177	5	2.8 (0.9–6.6)	.667	Reference			
	2017	574	10	1.7 (0.8–3.2)		0.68 (0.22–2.07)	0.493		
	2018	570	12	2.1 (1.1–3.7)		0.81 (0.27–2.10)	0.702		
Sex	Male	762	13	1.7 (0.9–2.9)	.311	Reference			
	Female	559	14	2.5 (1.3–3.9)		1.47 (0.68–3.18)	0.324		
Race	Black African	1301	27	2.1 (1.4–3.0)	.515	Reference			
	Non-black African	20	0	0.00					
Age group (months)	<1	108	3	2.8 (0.6–8.1)	.138	1.09 (0.28–4.29)	0.897	0.49 (0.09–2.76)	.416
	1 to <3	363	4	1.1 (0.3–2.8)		0.24 (0.07–0.80)	0.020	0.15 (0.04–0.63)	.010
	3 to <6	335	8	2.4 (1.0–4.7)		0.60 (0.23–1.60)	0.307	0.51 (0.18–1.44)	.200
	6 to <9	277	3	1.1 (0.2–3.2)		0.26 (0.07–0.97)	0.045	0.20 (0.05–0.82)	.025
	9 to <12	238	9	3.8 (1.7–7.2)		Reference		Reference	
Underlying condition[a]	No	1282	25	1.95 (1.3–2.9)	.167	Reference			
	Yes	39	2	5.1 (0.6–18.5)		5.48 (1.12–26.79)	0.036		
Malnutrition[b]	No	975	9	0.92 (0.4–1.8)	<.001	Reference		Reference	
	Yes	345	18	5.2 (3.1–8.3)		5.19 (2.29–11.79)	<0.001	4.80 (2.00–11.51)	<.001
	Unknown	1	0	0.0					
Feeding type	Exclusive breastfeeding	705	13	1.8 (1.0–3.2)	.946	Reference		Reference	
	Mixed feeding	240	5	2.1 (0.7–4.9)		1.04 (0.36–2.95)	0.948	1.02 (0.32–3.24)	.975
	Formula feeding	333	8	2.4 (1.0–4.7)		1.39 (0.57–3.40)	0.475	1.27 (0.48–3.35)	.634
	Unknown	43	1	2.3 (0.1–12.3)		1.30 (0.16–10.34)	0.802	0.57 (0.05–5.96)	.635
Prematurity[c]	No	1081	23	2.1 (1.4–3.2)	.648	Reference			
	Yes	240	4	1.7 (0.5–4.3)		0.76 (0.26–2.25)	0.618		
Birthweight[d]	Normal	970	21	2.2 (1.3–3.3)	.457	Reference			
	Low	280	6	2.1 (0.8–4.7)		1.01 (0.40–2.54)	0.986		
	Unknown	71	0	0.0					
Vaccination[e]	Full coverage	962	16	1.7 (1.0–2.7)	.253	0.49 (0.21–1.13)	0.095	0.20 (0.06–0.66)	008
	No full coverage	307	9	2.9 (1.3–5.6)		Reference		Reference	
	Unknown	52	2	3.9 (0.5–13.2)		1.35 (0.28–6.54)	0.713	0.62 (0.10–4.02)	.617
Admission diagnosis[f]	Non-respiratory	630	15	2.4 (1.3–3.9)	.663	Reference			
	Respiratory	682	12	1.76 (0.9–3.1)		0.64 (0.30–1.40)	0.264		
	Unknown	9	0	0.0					

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Table 2. Continued

Variable	Categories	Total, No. *N* = 1321	No. of deaths *N* = 27	Mortality ratio, % (95% CI)	*P*-value [g]	Odds ratio[h] (95% CI)	*P*-value	Adjusted OR[i] (95% CI)	*P*-value
Mothers/caregivers education level	None/Primary	616	18	2.9 (1.7–4.6)	.103	Reference		Reference	
	Secondary/Tertiary	692	9	1.3 (0.6–2.5)		0.61 (0.26–1.41)	0.244	0.77 (0.31–1.89)	.570
	Unknown	13	0	0.0					

[a]Underlying condition includes any of the following: asthma, chronic lung, heart, liver or renal disease, stroke, sinusitis, organ transplant, anemia, immunosuppressive therapy, splenectomy, diabetes, burns immunoglobulin deficiency, autoimmune disease, nephrotic syndrome, cancer, spinal cord injury, seizure disorder, cerebral palsy, congenital heart disease, other congenital disorder, obesity, or chronic gastrointestinal problems.

[b]Malnutrition defined as a weight-for-age <−2 standard deviations from the WHO mean *Z*-score.

[c]Prematurity defined as gestational age at birth of <37 weeks.

[d]Low infant birthweight defined as <2500 g.

[e]Vaccination defined as full vaccine coverage for age, using the *Haemophilus influenzae* type b vaccine given as part of the routine infant immunization schedule at 6, 10, 14 weeks as a proxy.

[f]Admission diagnosis: respiratory diagnosis includes apnea, neonatal sepsis, bronchiolitis, pneumonia, tuberculosis, and bronchitis and non-respiratory diagnosis includes encephalitis, viral illness, diarrhea, febrile seizures, meningitis, sepsis (non-neonatal), and other diagnosis.

[g]Chi-squared test *P*-value.

[h]Univariate mixed effects regression model, accounting for clustering by site.

[i]Multivariable mixed effects regression model, accounting for clustering by site.

malnutrition was identified as 1 of 2 most common underlying conditions among infant deaths [12].

Our study had a number of limitations. First, maternal HIV status was determined by numerous methods, including self-report for mothers living with HIV. It is possible that there was misclassification of infant's exposure status. Second, we did not determine whether the infant died subsequent to hospital discharge. Third, data were not collected for maternal characteristics that have been associated with increased infant mortality risk such as maternal health, vital status, and age and there may be residual confounding. Fourth, we may have been underpowered to detect an association between HIV exposure and mortality.

Strengthening efforts to further decrease vertical HIV transmission, such as early and repeat HIV testing of pregnant women and maintenance of maternal viral suppression, remain essential to prevent infant HIV infection. In addition, ensuring HI infants are diagnosed and started on treatment early, and that infants are well nourished and fully vaccinated will help to further reduce infant mortality.

Supplementary Data

Supplementary materials are available at the Journal of The Pediatric Infectious Diseases Society online (http://jpids.oxfordjournals.org).

Notes

Financial support. This work was supported by a research cooperative agreement with the United States of America Centers for Disease Control and Prevention (US CDC) [grant number 5U01IP001048]

Potential conflicts of interest. C. C. has received grant support from Sanofi Pasteur, the Bill and Melinda Gates Foundation, US CDC, South African Medical Research Council and Wellcome Trust. A. v. G. and N. W. have received grant funding from the US CDC, the Bill and Melinda Gates Foundation and Sanofi. J. M. has received grant funding from Sanofi Pasteur. C. V. M. has received grant funding from Pfizer. All other authors report no potential conflicts.

Author contribution: All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclaimer: The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their affiliated institutions or the agencies funding the study.

Acknowledgements

We acknowledge the following site investigators: Dr Omphile Mekgoe (Department of Paediatrics, Klerksdorp Hospital, Klerksdorp, South Africa), Dr Sumayya Haffejee (Department of Paediatrics, Matikwana Hospital, Hazyview, South Africa), Dr Fathima Naby (Department of Paediatrics, Pietermaritzburg Metropolitan Hospital, Pietermaritzburg, South Africa) and Dr Godfrey Siwele (Department of Medicine, Matikwana Hospital, Hazyview, South Africa), for the support they provided for the surveillance teams during participant enrollment.

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