Outcomes of HIV-exposed infected and HIV-exposed uninfected children admitted to two paediatric intensive care units in South Africa: A retrospective analytical cohort study

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Background. Reduced vertical transmission of HIV has led to an increased proportion of HIV-exposed uninfected children (HEU) in South Africa. Increased infective morbidity and mortality creates a need to better understand outcomes and morbidity in this population.

Objectives. To describe and compare critical care outcomes in terms of survival and disease severity between HIV-unexposed children (HUU), HIV-exposed infected children (HEI) and HEU.

Methods. A retrospective analytical cohort study was carried out from 1 January 2017 to 31 December 2021. Paediatric intensive care unit admissions of children aged 1 month - 5 years were included. Outcomes for HEU and HEI were compared with those of HUU, with a significance threshold set at p=0.05. Multivariate logistic regression analysis was conducted.

Results. Of 1 015 children, 633 (62.4%) were HUU, 318 (31.3%) were HEU and 64 (6.3%) were HEI. Mortality was higher in HEU (15.8%; p=0.1) and HEI (17.2%; p=0.4) compared with HUU (11.4%), but this was not statistically significant. HEU and HEI were younger (p<0.001) and more frequently underweight (p<0.001). HEU (and HEI) had an increased risk of acute kidney injury (AKI) (odds ratio 1.19; 95% confidence interval 1.07 - 1.81; p=0.014) and a lower minimum estimated glomerular filtration rate (p<0.001) compared with HUU. Septic shock was more frequent in HEU (28.6%; p=0.001) and HEI (43.8%; p<0.001) compared with HUU (20.1%). HEI had more frequent mechanical ventilation (p=0.003), more prolonged mechanical ventilation (p<0.001) and lower admission haemoglobin concentrations (p<0.001) than HUU.

Conclusion. Compared with HUU, both HEU and HEI demonstrated a trend towards increased mortality, but this was not statistically significant. HEU and HEI experienced increased AKI and other morbidity.

Keywords. HIV exposed uninfected, paediatric critical care, outcomes, acute kidney injury.

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Contribution of the study

This study provides the largest report of outcomes in HIV-exposed uninfected children (HEU) to date. The study provides new data suggesting that HEU may be at increased risk of acute kidney injury.

The past two decades were marked by reductions in vertical transmission of HIV. Thanks to improved antiretroviral therapy (ART) for pregnant and breastfeeding women, improved infant ART prophylaxis and emphasis on breastfeeding, children born to HIV-infected women are now 30 times less likely to become vertically infected than in 2003.[1]

HIV-exposed uninfected children (HEU) outnumber the HIV-exposed infected population (HEI). South Africa (SA) is home to ~20 million children, of whom 5 - 6 million (25 - 30%) are HEU[2-4] and just over 200 000 (~1%) are HEI.[5]

Increased infective morbidity and mortality, especially in early infancy, increase frequency of hospitalisation and severity of disease in HEU. Meta-analysis has demonstrated an increased risk of diarrhoea and pneumonia in HEU compared with HIV-unexposed children (HUU), and the risk of mortality at 2 years was approximately double that of HUU.[2,6-11]

Single-centre studies have investigated the role of HIV exposure and infection in paediatric intensive care units (PICUs), although most have been small. While these did not demonstrate a difference in mortality based on HIV exposure, they demonstrated prolonged mechanical ventilation and length of stay in HEU and HEI.[12] In 2023, Whitehead and Ballot[13] reported the largest study comparing HEU, HEI and HUU to date. Of 678 children, 109 (16%) were HEU and 35 (5.2%) were HEI. The authors reported higher mortality in HEI (40%; p=0.02) compared with HIV-negative children (22.7%), which was not present when

comparing only children with non-surgical diagnoses (p=0.27). They found no difference in length of PICU stay, ventilation or mortality in HEU compared with HUU.

Research on HEU is a priority in low- to middle-income countries, where the majority of HEU live[14] and critical care resources are constrained. Patterns of morbidity and mortality in critically ill HEU may reveal targets for interventions to improve outcomes. In this study, we aimed to investigate the outcomes of HIV-exposed children compared with HIV-unexposed children in two tertiary PICUs.

Methods

Study design and setting

A retrospective analytical cohort study at two tertiary-level PICUs in Mangaung, Free State, SA, was conducted. Each PICU has 5 beds and serves as a multidisciplinary unit for paediatric patients from medical and surgical disciplines, including general surgical, neurosurgical, trauma, burns and cardiothoracic patients. These PICU services provide invasive and non-invasive respiratory support, cardiovascular support, multimodal invasive and non-invasive monitoring, and renal replacement therapy. Patient selection for PICU admission is individualised on the basis of available resources, the presence of a treatable, life-threatening condition, and the requirement for a clinical service only available in a PICU.

Case definitions

HIV status

HUU were defined by a documented negative maternal HIV test (HIV enzyme-linked immunosorbent assay (ELISA) or point-of-care test) at the time of admission, with or without a documented negative HIV test (HIV polymerase chain reaction (PCR) for children aged <18 months, HIV ELISA or point-of-care test for those aged >18 months) for the child.

HEU were defined as children with a documented negative HIV test at the time of admission and maternal HIV infection, either by a documented positive HIV test or from previous medical records.

HEI were defined as children who had a positive HIV test at the time of admission or a previously documented positive HIV test.

Weight for age

Patients who had estimated weights were categorised as 'not recorded'. Only patients with measured weights were classified using the weight-for-age World Health Organization z-score charts.

Septic shock

Septic shock was defined as severe infection with cardiovascular dysfunction (hypotension, impaired perfusion, or need for vasoactive medication). Nosocomial infection was defined by physician-reported infection or initiation of antimicrobial therapy for a proven or presumed infection acquired in the PICU.

Paediatric Index of Mortality

The Paediatric Index of Mortality 3 (PIM3) score is a validated mortality risk tool used in PICUs worldwide to estimate severity of illness.[15] The PIM3 score uses physiological variables (systolic blood pressure, fraction of inspired oxygen, arterial partial pressure of oxygen, and base excess) collected within the 1st hour of PICU admission and other variables to predict risk of mortality. The standardised mortality rate (SMR) is the calculated ratio of observed deaths to predicted deaths from the PIM3 score and is used as an estimate of quality of care in a PICU.

Acute kidney injury

Acute kidney injury (AKI) was defined as stage 1 or greater according to the Kidney Disease: Improving Global Outcomes (KDIGO) staging.[16] The estimated glomerular filtration rate (eGFR) was calculated using the bedside Schwarz formula.

Study population

Children aged 1 - 60 months admitted to the PICUs between 1 January 2017 and 31 December 2021 were included. Patients whose HIV status could not be determined by the researcher and those who were admitted for <24 hours for elective postoperative monitoring were excluded. After exclusion criteria were applied, 1 015 patients were included as study participants. A summary of participant selection is shown in Fig. 1.

Data collection

Data were collected from the electronic hospital record system. Data were entered directly into REDCap (Research Electronic Data Capture), a secure electronic research database hosted at the University of the Free State. Once all data had been collected, the data set was exported as a .csv file to a biostatistician for data analysis.

Outcomes

We investigated mortality, length of PICU stay, need for mechanical ventilation, duration of mechanical ventilation, AKI, and need for vasoactive medications as outcome variables. Multivariate logistic regression methods were used to derive odds ratios (ORs), hazard ratios (HRs) and incidence rate ratios (IRRs), as well as 95% confidence intervals (CIs). The HUU population served as the reference group, and the risk of non-mortality outcomes was adjusted for disease severity (predicted PIM3 mortality risk) in HEUs and HEIs, reported as ORs, HRs and IRRs (see Table 3).

Data analysis

Descriptive analysis was conducted for all variables. Categorical variables were presented as frequencies and percentages, and numerical variables were presented as medians and interquartile ranges (IQRs). We used the Shapiro test to determine whether the continuous variables were skewed. For comparisons, we used the Wilcoxon rank-sum test for continuous variables, and Pearson's χ^2 test and Fisher's exact test for categorical variables. Outcome analysis and risk estimation were conducted using regression techniques, including the Cox proportional hazards model and multivariate logistic regression to estimate the effect of the level of HIV exposure on outcomes and to adjust for the appropriate variables including HIV exposure as a primary predictor. Results from the multivariate analysis were summarised using coefficients and 95% CIs. An association was considered statistically significant if the p-value was <0.05.

Ethical considerations

Approval was obtained from the University of the Free State Health Sciences Research Ethics Committee (ref. no. UFS-HSD2022/0499/2510). The study was approved by the Free State Department of Health (ref. no. FS_202209_001). As this was a low-risk, retrospective study, the requirement for informed consent from participants and caregivers was waived.

Results

Descriptive data

Most participants (62.4%; n=633) were HUU. HEU participants made up 31.3% of the study population (n=318). Further descriptive data are presented in Table 1.

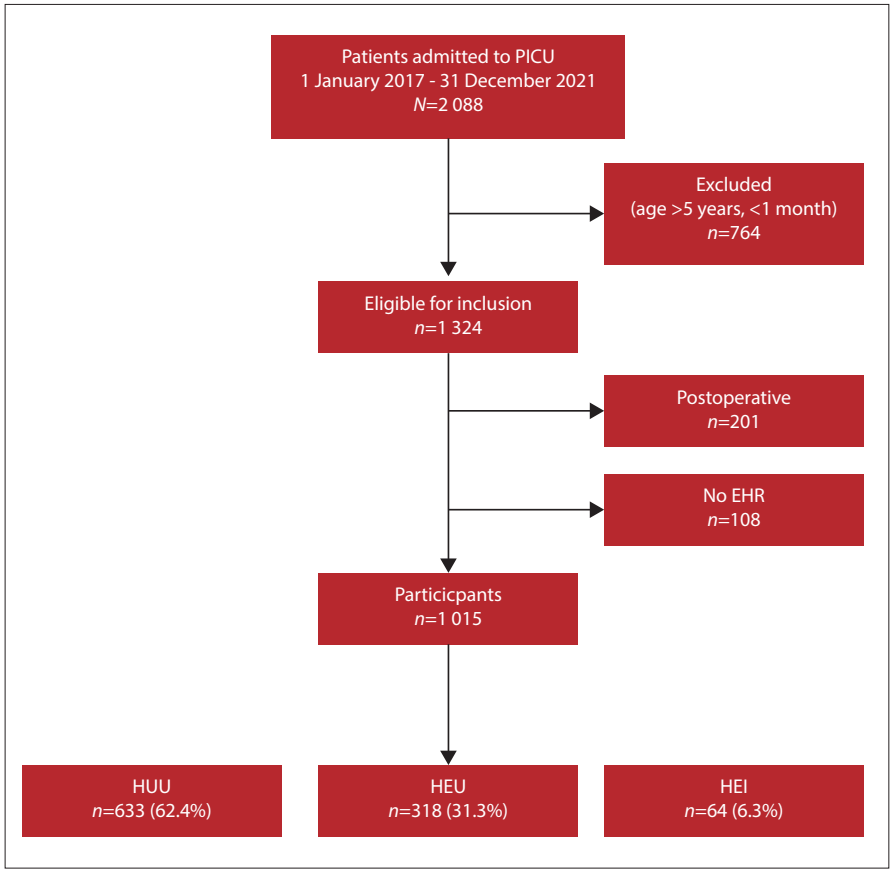

Fig. 1. Participant selection process. (PICU = paediatric intensive care unit; EHR = electronic hospital record; HUU = HIV unexposed; HEU = HIV exposed uninfected; HEI = HIV exposed infected.)

Of the HEI, 57.8% were newly diagnosed in the PICU. A further 4 children (6.3%) were known to be HEI but had interrupted ART. Viral loads were known for 39 (60.9%) of HEI, with only 3 (7.7%) having a viral load <1 000 copies/mL. Forty-three (67.2%) had a recorded CD4 count, with 12 (27.9%) having a CD4 >25%.

Prevention of mother-to-child transmission (PMTCT) data were available in the records of 29 HEI (45.3%) and 171 HEU (53.8%). PMTCT was completed or ongoing in 16 HEI (55.2%) and 152 HEU (88.9%). No or partial PMTCT had been provided to 7 (24.1%) and 6 (20.1%) HEI, respectively, and to 4 (2.6%) and 15 (9.9%) HEU, respectively.

Outcome findings

Outcome data are presented in Table 2. In total, 133 of the 1 015 participants died, so overall mortality was 13.1%. The SMR for HUU was 1.1 as opposed to 1.7 for HEU and 2.1 for HEI.

A microbiologically confirmed diagnosis of tuberculosis was made in 14 HEI (21.9%) and 10 HEU (3.1%). *Pneumocystis jirovecii* pneumonia (PJP) was confirmed by positive PCR in 9 (14.1%) of the HEI and 2 (0.6%) of the HEU. A further 30 HEI (46.9%) and 17 HEU (5.3%) were treated empirically for suspected PJP without a positive PCR. Twenty-four HEI (47.5%) and 7 HEU (2.2%) had a cytomegalovirus (CMV) viral load >10 000 copies/mL or were treated for CMV. A further 18 HEI (21.8%) and 22 HEU (6.9%) had a CMV viral load between 1 000 and 10 000 copies/mL and did not receive treatment.

Regression analysis

The results of the logistic regression analysis are presented in Table 3.

Discussion

To our knowledge, this study is the largest observational study of critical care outcomes in HEU. The largest study prior to this was that of Whitehead and Ballot.[13] Other smaller studies only included children with lower respiratory tract infections,[12,17,18] limiting our ability to compare patient profiles.

Descriptive findings

HEU accounted for 31.3% of PICU admissions. This figure is similar to contemporary PICU studies[12,17,18] and in keeping with the estimated proportion of HEU in the total SA paediatric population.[1,3,5]

HEU and HEI were younger than HUU and more frequently underweight. The former finding is in keeping with the findings of Whitehead and Ballot,[13] who reported a median (IQR) age of 3 (6) months in HEU as opposed to 13 (51) months in HUU. This difference probably reflects early presentation with severe illness in HEI and HEU. While the analysis of weight was confounded by high and varying rates of missing data, our findings are in keeping with those of Whitehead and Ballot,[13] who found lower weight *z*-scores in HEU compared with HUU (p=0.001).

Outcomes

Larger proportions of HEU and HEI died compared with HUU. While this was not statistically significant, the trend reflects the findings of Whitehead and Ballot,[13] who reported a statistically significant increase in mortality in HEI and a trend towards increased mortality in HEU. While HEI had prolonged mechanical ventilation and length of stay, this effect was not demonstrated in HEU. These results are in keeping with similar studies.[12,17,18] While meta-analysis has demonstrated conflicting results regarding mortality and intra-study heterogeneity exists, a trend is apparent towards mortality in HEU compared with HUU.[19]

Both HEI and HEU had lower haemoglobin concentrations than HUU, but the difference in HEU was moderate at 0.4 g/dL lower than HUU and is likely to be of limited clinical significance. A recent study of HEU outpatients did not demonstrate a difference in the prevalence of anaemia or haemoglobin concentrations compared with HUU.[20]

Septic shock was more frequent in HEI and HEU than HUU. While there was a trend towards more frequent use of vasoactive medication, this was not statistically significant. The rate of nosocomial infections was high overall (28.7%), and was statistically significantly higher in the HEI group compared with the HUU. However, this rate is lower than the 44% reported in a Moroccan study in 2024.[21]

A study comparing PIM2 scores of patients admitted with pneumonia demonstrated that both HEI and HEU had statistically significant increased predicted mortality (p<0.001).[18] The increased SMR in HEU and HEI in the present study compared with an SMR of close to 1 in HUU suggests that HEU and HEI experience excess mortality despite similar care. While the reason for this finding is unknown, it may reflect different host factors or the greater frequency of nosocomial infections in HIV-exposed children. Further research is required to better understand it.

Table 1. Descriptive data of study participants (*N*=1 015)

	HUU (*n*=633; 62.4%), *n* (%)*	HEI (*n*=64; 6.3%), *n* (%)*	*p*-value	HEU (*n*=318; 31.3%), *n* (%)*	*p*-value
Age (months), median (IQR)	7 (2 - 20)	4 (3 - 13)	0.3	4 (2 - 12)	<0.001
Sex			>0.9		>0.9
Male	365 (57.7)	37 (57.8)		189 (59.4)	
Female	268 (42.3)	27 (42.2)		129 (40.6)	
Prematurity	109 (17.2)	13 (20.3)	0.6	65 (20.4)	0.11
Weight for age (*z*-score)			<0.001		<0.001
<–3	101 (16.0)	15 (23.4)		78 (24.5)	
–3 - –2	70 (11.1)	16 (25.0)		52 (16.4)	
–2 - 0	223 (35.2)	22 (34.4)		110 (34.6)	
0 - 2	122 (19.3)	6 (9.4)		30 (9.4)	
2 - 3	16 (2.5)	0		4 (1.3)	
>3	5 (0.8)	0		8 (2.5)	
Not recorded	96 (15.2)	5 (7.8)		36 (11.3)	

HUU = HIV unexposed; HEI = HIV exposed infected; HEU = HIV exposed uninfected; IQR = interquartile range.
*Except where otherwise indicated.

Table 2. Primary outcomes of study participants (*N*=1 015)

	HUU (*n*=633; 62.4%), *n* (%)*	HEI (*n*=64; 6.3%), *n* (%)*	*p*-value	HEU (*n*=318; 31.3%), *n* (%)*	*p*-value
Discharge outcome			0.4		0.1
Discharged from PICU	527 (83.3)	51 (79.7)		256 (80.8)	
Death before PICU discharge	72 (11.4)	11 (17.2)		50 (15.8)	
Transfer to other PICU	21 (3.3)	2 (3.1)		9 (2.8)	
Outcome unknown	13 (2.1)	0		2 (0.6)	
PIM3 score, median (IQR)	0.03 (0.02 - 0.08)	0.05 (0.03 - 0.10)	0.005	0.04 (0.02 - 0.08)	0.13
Length of stay (days), median (IQR)	5.0 (3.0 - 8.0)	9.0 (4.8 - 16.3)	<0.001	5.0 (3.0 - 9.0)	0.9
Mechanical ventilation	332 (52.4)	47 (73.4)	0.003	167 (52.5)	>0.9
Ventilator days, median (IQR)	4.5 (2.0 - 8.0)	9.0 (6.0 - 13.5)	<0.001	5.0 (3.0 - 8.0)	0.3
Hypovolaemic shock	152 (24.0)	18 (28.1)	0.6	82 (25.8)	0.3
Septic shock	127 (20.1)	28 (43.8)	<0.001	91 (28.6)	0.001
Vasoactive medication required	181 (28.6)	31 (48.4)	0.4	115 (36.2)	0.4
Minimum eGFR (mL/kg/m^2), median (IQR)	52 (30 - 86)	32 (22 - 54)	0.005	36 (19 - 64)	<0.001
AKI staging			0.001		0.007
No AKI	372 (59.1)	23 (35.9)		154 (49.7)	
Stage 1	119 (18.9)	15 (23.4)		61 (19.7)	
Stage 2	90 (14.4)	19 (29.7)		53 (17.1)	
Stage 3	48 (7.6)	7 (11.0)		42 (13.5)	
Hb on admission, median (IQR)	10.6 (9.20 - 11.88)	9.4 (7.98 - 10.23)	<0.001	10.2 (8.8 - 11.6)	0.028
Nosocomial infection	163 (25.8)	35 (54.7)	<0.001	93 (29.2)	0.5

HUU = HIV unexposed; HEI = HIV exposed infected; HEU = HIV exposed uninfected; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3; IQR = interquartile range; eGFR = estimated glomerular filtration rate; AKI = acute kidney injury; Hb = haemoglobin.
*Except where otherwise indicated.

In the present study, HEI experienced increased morbidity in the PICU, with prolonged length of stay and increased need for and duration of mechanical ventilation. These findings reflect those in other PICU studies in the era where universal ART is standard of care,[12,17,18] and are relevant in terms of the large number of HEI patients in our study (despite missing data) who had not completed PMTCT, were not diagnosed with HIV by the time of presentation, were not on ART at admission, and were not virologically suppressed. These failures are an important target for programmatic improvement, given the increased burden on scarce resources.

Acute kidney injury

Key findings were the increased likelihood of HEU and HEI developing AKI and a lower minimum eGFR in HEU compared with HUU. These findings may be related to the relatively higher rates of septic shock in HEU and HEI. The crude incidence of AKI (44.7%) was higher than other reports of incidences between 10% and 40%.[22,23] It is higher than the incidence of 26.9% reported by the multinational AWARE (Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology) study, which did not include any PICU in Africa.[23] We could not find any studies describing HIV exposure as a risk factor for the development of AKI.

Several research gaps arise from the present study. Further research is required to define the prevalence, long-term outcomes and pathobiology of AKI in critically ill HEU and HEI. Multicentre studies are needed to better define the influence of HIV exposure and infection on PICU

Table 3. Outcomes compared with HUU adjusted for disease severity

	HEU			HEI		
	OR*	95% CI	*p*-value	OR*	95% CI	*p*-value
Mortality	1.33†	0.92 - 1.92	0.13	1.02†	0.54 - 1.95	>0.9
Mechanical ventilation	0.94	0.71 - 1.24	0.7	2.44	1.39 - 4.47	0.003
Ventilator days	1.03‡	0.96 - 1.11	0.4	1.59‡	1.44 - 1.76	<0.001
AKI	1.39	1.07 - 1.81	0.014	2.17	1.36 - 3.45	0.001
Minimum eGFR	−8.6§	−15 - −1.8	0.013	−11	−23 - 0.89	0.071
Vasoactive medication required	1.5	0.92 - 2.46	0.11	1.78	0.80 - 4.39	0.2
Length of stay	0.98‡	0.93 - 1.04	0.5	1.54‡	1.42 - 1.67	<0.001

HUU = HIV unexposed; HEU = HIV exposed uninfected; HEI = HIV exposed infected; OR = odds ratio; CI = confidence interval; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate.
*Except where otherwise indicated.
†Hazard ratio.
‡Incidence rate ratio.
§Beta coefficient.

outcomes. Studies on mortality risk prediction and SMR in HEU and HEI would assist in improving benchmarking of care in this population. Interventional studies on the treatment of HEU and HEI are required to tailor therapy better to their needs.

Study limitations

Owing to the retrospective design of the study, missing data was a limitation. Weight was the only anthropometric variable recorded, with varying frequencies of missing weight data between groups limiting the strength of this comparison. The inclusion of contemporary maternal HIV tests in the HEU definition is likely to have led to children who were not HIV exposed *in utero* or during birth being included in the HEU group. This inclusion introduces additional heterogeneity and limits analysis. Further investigation of mechanical ventilation and high-frequency oscillation would have been a useful marker of severity and point of comparison. Data were not collected on independent risk factors for AKI. We did not collect outcome data on patients transferred out, which may have influenced the analysis of mortality risk. We also did not collect diagnostic data which may have provided insights into patient subgroups. Septic shock and nosocomial sepsis require clear definitions such as those provided by the Phoenix criteria (published after data collection) to provide explicit standards for the estimation of their prevalence.[24] The absence of opportunistic infection data in the HUU group limited our analysis of opportunistic infections. Similarly, PMTCT and other HIV data were under-reported in the medical records.

Conclusion

This research is one of the largest investigations of the effect of HIV exposure on PICU outcomes. Both HEI and HEU were at increased risk of AKI and other morbidity compared with HUU. There was a trend towards increased mortality in HEU and HEI, but this was not statistically significant. HEI had increased need for mechanical ventilation, duration of mechanical ventilation and length of stay. Larger multicentre studies are required to better understand the influence of HIV exposure without infection on critical illness.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (MAP) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.

Declaration. The research for this study was done in partial fulfilment of the requirements for MvdM's MMed (Paed) degree at the University of the Free State.

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Author contributions. MvdM was the principal investigator, conceptualised and designed the study, conducted data collection and prepared the manuscript. JBS contributed to the study design, conducted the statistical analysis and provided critical inputs to the manuscript. MAP provided research supervision for the MMed project, contributed to study conceptualisation and design, assisted with data analysis and contributed to the manuscript.

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