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A Retrospective Observational Study of The Impact of HIV Status on The Outcome of Paediatric Intensive Care Unit Admissions

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A Retrospective Observational Study of The Impact of HIV Status on The Outcome of Paediatric Intensive Care Unit Admissions

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A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg as part of the requirements for the degree of Master of Medicine in Paediatrics

Johannesburg, December 2022

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DECLARATION

I, Kim Whitehead, declare that this research report is my own work and has not been submitted before for any degree or examination at this or any other university. It is being submitted for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg.

Signature: 

Date: 6th day of December 2022

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LIST OF ABBREVIATIONS

A,D & P	Accidents, drownings and poisonings
ART	Antiretroviral Therapy
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
CPAP	Continuous Positive Airway Pressure
ELISA	Enzyme-Linked Immunosorbent Assay
HEU	HIV Exposed Uninfected
HFOV	High Frequency Oscillatory Ventilation
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IPPV	Intermittent Positive Pressure Ventilation
IQR	Interquartile Range
LDH	Lactate Dehydrogenase
LMICs	Low and Middle Income Countries
LRT	Lower Respiratory Tract
PCP	Pneumocystis pneumonia
PCR	Polymerase Chain Reaction
PICU	Paediatric Intensive Care Unit
PIM3	Paeditric Index of Mortality 3
PJP	Pneumocystis jirovicii Pneumonia
PMTCT	Prevention of Mother to Child Transmission
REDCap	Research Electronic Data Capture
SPSS	Statistical Programme for the Social Sciences
WHO	World Health Organization

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Retrospective Observational Study of The Impact of HIV Status on The Outcome of Paediatric Intensive Care Unit Admissions

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ABSTRACT *(347 words)*

BACKGROUND: Previously it was thought futile to offer HIV infected children ICU care, however this has changed with the availability of Antiretroviral Therapy (ART). Improved Prevention of Mother to Child Transmission (PMTCT) has led to a larger population of HIV exposed uninfected (HEU) children with unique health risks. Our study looked at how HIV exposure and infection impact presentation and outcomes in PICU in an era of improved access to ART and PMTCT.

METHODS: A retrospective analysis of children admitted to PICU at a tertiary/quaternary hospital between 2015 and 2019 was conducted. De-identified data was obtained from an existing database and analysed using SPSS software. Medians and interquartile ranges were used to analyse continuous variables and frequencies and percentages to analyse categorical variables. The sample was then divided into three groups (HIV negative, HEU and HIV infected) and their presentation and outcomes compared using Chi-Squared and Kruskall-Wallis tests with a significance level set at $p < 0.05$.

RESULTS: Our study showed that 16% (109/678) of children admitted to PICU were HEU and 5.2% (35/678) HIV infected. HIV infected children were admitted at a younger age (median two months) and had an increased incidence of lower respiratory tract infections than HIV negative children ($p < 0.001$). HIV infected children required longer ventilation and admission than HIV negative and HEU children ($p < 0.001$). HIV infected children had a higher mortality (40%) ($p = 0.02$) than HIV negative children (mortality 22.7%); when comparing children admitted with a medical diagnosis however the difference in mortality was not statistically significant ($p = 0.273$). HEU children were admitted at a younger age (median three months) with a higher incidence of lower respiratory tract conditions than HIV negative children ($p < 0.001$). HEU children had similar outcomes to HIV negative children with no statistically significant difference in duration of ICU stay ($p =0.163$); ventilation ($p = 0.443$) or mortality ($p=0.292$).

CONCLUSION: HIV infected children presented with more severe disease requiring longer ventilation and admission. HEU had similar outcomes to HIV negative children.

KEYWORDS: Human Immunodeficiency Virus, Paediatric Intensive Care Unit, Outcomes

BACKGROUND

Human Immunodeficiency Virus (HIV) remains an important healthcare problem. Despite the introduction of expanded Prevention of Mother to Child Transmission (PMTCT) programmes and universal access to Antiretroviral Therapy (ART) HIV still accounts for 1.2 – 8.7% of under-five deaths in South Africa (1). South Africa has reduced its mother to child transmission from 16% in 2010 to 3.3% in 2019 resulting in a growing population of children who are HIV exposed but uninfected (HEU) (2, 3). In 2019 there were an estimated 290 000 children living with HIV, 3 700 HIV-related deaths in children and 3.9 million HEU children in South Africa (2).

Currently in South Africa only 51% of HIV infected children are on ART (2). HIV infected children not yet on treatment often present to a healthcare facility with an acute severe illness requiring Paediatric Intensive Care Unit (PICU) admission as their first presentation (4, 5). At the start of the HIV epidemic, admission of HIV infected children into PICU was considered futile in view of a mortality as high as 84 -100%, ventilation showing no benefit and there being little hope of cure (6-8). As the epidemic evolved ART became more readily available and treatment and ventilation strategies for opportunistic infections improved. This led to improved outcomes with several studies showing no difference in mortality between HIV infected and HIV negative children (4, 5, 9-11). In view of this HIV is no longer a reason to deny a child admission to PICU (5, 12).

HIV infected children are most often admitted to PICU with acute respiratory tract infections but may also present with multi-organ involvement. Opportunistic infections such as Pneumocystis pneumonia (PCP) and cytomegalovirus (CMV) increase mortality to up to 50% despite the availability of antimicrobials for these diseases (4, 13-15). The growing population

of HEU children is also important as HIV exposure increases the risk for severe pneumonia and opportunistic infections with a proportion of these children requiring PICU admission (16). Although HIV exposure has not been shown to increase mortality in PICU these patients may have a significantly longer stay in PICU (10, 11). This is likely to place an additional burden on limited PICU resources.

PICU is a limited resource in South Africa with only 19.6% of public ICU beds allocated to neonatal and paediatric patients (17). Ethical dilemmas arise regarding which patients to accept to PICU in view of the limited beds and occupancy levels of 97% (12). There are currently no national guidelines on allocation of PICU beds, therefore hospitals draw on international guidelines or set up their own admission guidelines (12). There is a need for low and middle income countries (LMICs) to develop their own critical care guidelines based on available resources and disease spectrum while being guided by the local context (18).

Statistics on the mortality rate in HIV infected children admitted to PICU are still conflicting ranging from 11 - 31.3% depending on the centre (9-11). Further studies are required to ascertain how HIV infection and exposure impact on presentation and outcomes in PICU in the era of improved access to ART and PMTCT. This will allow for the motivation of more resources for PICU and HIV programmes and assist with drawing up PICU admission guidelines. The aim of this study was therefore to compare the characteristics and outcomes of HIV negative, HEU and HIV infected children admitted to PICU.

METHODS

Study design

This was a secondary analysis of an existing database. The database was created by capturing data on discharge from PICU for the purpose of quality improvement and managed by the Research Electronic Data Capture (REDCap) system hosted by the University of the Witwatersrand (19). The data was collected prospectively on discharge of patients with several checkpoints.

Study Setting

The study was based at the PICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa. CMJAH is a tertiary/quaternary hospital that provides healthcare to the Gauteng population as well as some of the neighbouring provinces and countries where tertiary services are not available. At the time of the study CMJAH had 14 shared neonatal and PICU beds, these beds are in high demand by both medical and surgical specialities. Usually, only children requiring invasive ventilation are admitted to this centre's PICU.

Participants

All children between the age of 29 days and 12 years 11 months admitted to the PICU at CMJAH between January 2015 and December 2019 were eligible for inclusion in this study. Children with missing records or in whom the HIV results were unknown were excluded. If children were readmitted, each admission was counted separately in the study.

Study Procedure

We retrieved de-identifed data for the study period from the CMJAH PICU database. De-identified data was imported into an Excel spreadsheet and the inclusion and exclusion criteria were applied.

We captured demographic data, namely gender and admission age in months. We classified the HIV status as follows (3, 20):

1) HIV negative: The mother was negative, or the child had a negative HIV ELISA
2) HEU: The mother was HIV positive or the child less than 18 months had a positive ELISA AND the child had a negative HIV PCR
3) HIV infected: A child less than 18 months with a positive HIV PCR or a child more than 18 months with a positive ELISA. HIV infection was confirmed with a second ELISA, PCR or HIV Viral Load

HIV exposed children include both HEU and HIV infected children.

We captured clinical data consisting of weight, height, admission diagnosis, ventilation and inotropic support, opportunistic and other infections. Weight z-scores were calculated using weight in kilograms and WHO growth charts (21). Height was not analysed as it was often not recorded. The admission diagnosis was the reason for requiring ICU and was classified into 4 groups:

1) Surgical: any patient admitted with an underlying surgical condition
2) Accidents (including trauma), drownings and poisonings (A,D +P)
3) Lower respiratory tract (LRT) conditions: an illness affecting the respiratory tract below the level of the larynx including pneumonia, bronchiolitis, asthma, and pleural effusions.
4) Other medical conditions: Medical conditions other than lower respiratory tract conditions (e.g. gastrointestinal and cardiovascular conditions).

Patients were classified as being post-operative if they were admitted to the PICU after a surgical procedure. The ventilatory mode was defined as the maximum level of ventilatory

support required: continuous positive airway pressure (CPAP), intermittent positive pressure ventilation (IPPV) or high frequency ventilation (HFOV).

Opportunistic and other infections were diagnosed as follows. Pneumocystis pneumonia (PCP) was a clinical diagnosis supported by laboratory markers such as lactate dehydrogenase (LDH), beta-D-glucan and *Pneumocystis jirovecii* polymerase chain reaction (PCR). Cytomegalovirus (CMV) was suspected clinically in HIV exposed or infected children admitted with severe pneumonia and confirmed with a CMV Viral Load of more than 10 000. Tuberculosis was diagnosed either on clinical and X-ray findings or with a GeneXpert and TB microscopy and culture. Bacterial and fungal infections were defined by positive blood cultures. Viral infections (excluding HIV) included influenza, respiratory syncytial virus (RSV), adenovirus and other respiratory viruses as well as CMV and were confirmed by viral PCR on respiratory swabs and CMV viral loads.

The outcome measures we looked at were duration of ventilation, length of PICU admission and death in PICU.

The study population was then divided into three groups namely HIV infected, HEU and HIV negative. A comparison of the demographics, clinical data and outcomes was done between these three groups. Further analysis was then done by excluding children admitted with a surgical condition or due to accidents, drownings and poisonings, as the majority of these groups did not have HIV and this could bias the sample.

Statistical Methods

Data analysis was performed using SPSS software (Version 27). Only valid cases were analysed for each variable (i.e. missing information was excluded). Descriptive statistics revealed a skewed distribution of all the continuous variables therefore medians and interquartile ranges (IQR) were used to describe them. Frequencies and percentages were used to describe categorical variables.

The comparison between the HIV negative, HEU and HIV infected groups was done using the Chi-Squared test to compare categorical variables. If there was a significant difference a second analysis between HIV infected and HIV negative; HEU and HIV infected and HEU and HIV negative groups was done separately to see which groups accounted for the difference. In view of the skewed distribution the Kruskall-Wallis test was used to compare continuous variables between these three groups. The adjusted significance using the Bonferroni correction was used when the individual groups were compared. The significance level was set at $p < 0.05$.

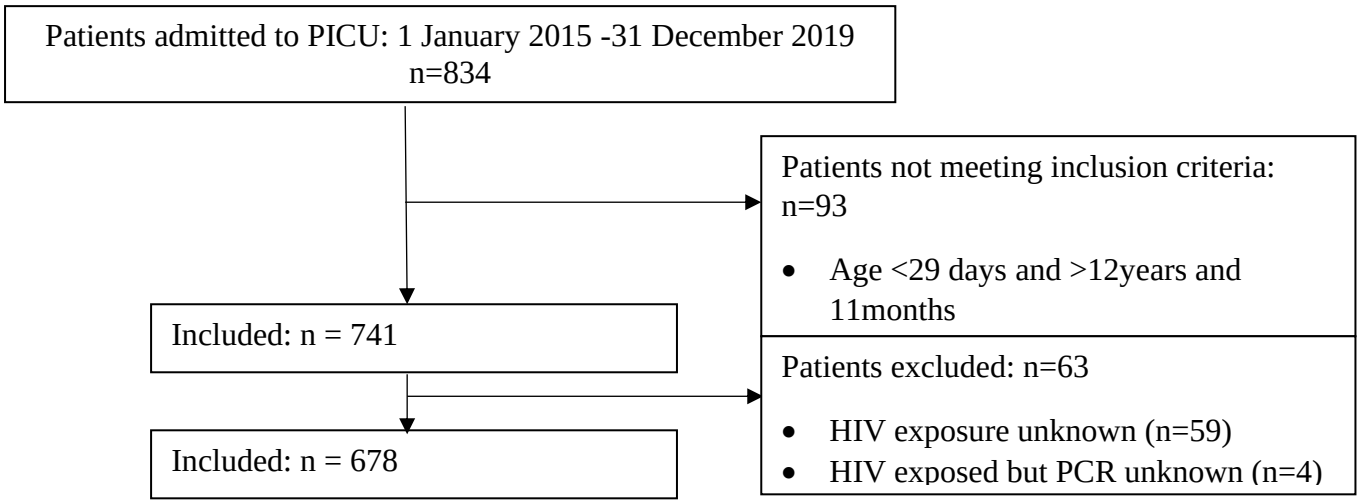
Ethical Consideration

The Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate M200436) as well as the clinical manager at CMJAH approved the study. Due to the retrospective nature of the study no informed consent was obtained.

RESULTS

A total of 834 children were admitted to the PICU at CMJAH, from 1 January 2015 to 31 December 2019. Our final sample size was 678 (see Figure 1).

Figure 1: Flow diagram of Participants in the Retrospective Observational Study of the Impact of HIV Status on the Outcome of PICU admissions



HIV status of the participants in the study were as follows: 534/678 (78.8%) were HIV negative and 144/678 (21.2%) were HIV exposed. In the HIV exposed group 35/144 (24.3%) were HIV infected and 109/144 (75.7%) were HIV exposed uninfected (HEU). In total 5.2% (35/678) of the admissions were HIV infected.

The median age of the children admitted to the PICU was eight months with an interquartile range (IQR) of 42 months (First quartile (Q1) two months and third quartile (Q3) 44 months). Females made up 46.8% (317/678) of the sample; males made up 53.1% (360/678) and the remaining 0.1% (1/678) were intersex. The median weight z-score of children admitted to PICU was -1.73 (IQR 3.44(Q1 – 0.23; Q3 -3.67)).

Patients admitted to the PICU had a wide variety of diagnoses on admission with the majority having a primary surgical diagnosis 298/678 (44%), followed by lower respiratory tract conditions 172/678 (25.4%). The remainder of patients were admitted with other medical

conditions (121/678 (17.8%)) and following accidents, poisonings and drownings (87/678 (12.8%)). Forty eight percent (317/668) of patients were admitted to PICU post-operatively. Most patients, 619/673 (92%) were intubated and ventilated. The majority were treated with IPPV 532/654 (81.3%) while 43/654 (6.6%) required HFOV and 19/654 (2.9%) required CPAP. Inotropic support was given to 129/671 (19.2%) of patients.

Bacterial infections were diagnosed in 115 patients (17.6%), viral infections in 51 patients (7.8%) and fungal infections in 14 patients (2.1%). The most common organisms cultured were Coagulase Negative Staphylococcus (CNS) (these were likely to have been contaminants) followed by *Staphylococcus aureus* and Gram Negative organisms (*Acinetobacter* species and *Klebsiella* species). The most common viral infection was Respiratory Syncytial Virus (21/657, 3.2%), and multiple viral organisms were found in 3/657 (0.5%) of patients.

Patients were ventilated and admitted to PICU for a median of three days (IQR of eight). The mortality rate in PICU was 24.8% (167/673) during our study period.

COMPARISON BETWEEN HIV NEGATIVE, HEU AND HIV INFECTED PATIENTS

HIV impacted on the age of admission ($p < 0.001$), weight z-score ($p < 0.001$), admission diagnosis ($p < 0.001$)) when doing an overall comparison between the three groups. HIV status also impacted on the occurrence of TB ($p < 0.001$), viral infections ($p < 0.001$) and PCP/CMV ($p < 0.001$). HIV status affected outcomes in terms of duration of ventilation ($p < 0.001$), length of ICU stay ($p < 0.001$) and mortality ($p = 0.025$). There was no statistically significant difference between the three groups for gender ($p = 0.988$), incidence of bacterial ($p = 0.160$) or fungal ($p = 0.645$) infections and need for ventilation ($p = 0.179$) or inotropic support ($p =$

0.689). Tables 1 to 3 compare HIV negative, HIV infected and HEU groups for variables where there was a significant overall p -value between the three groups.

Table 1: Comparison of HIV Negative and HIV Infected patients admitted to the PICU

	HIV Negative	HIV Infected	p-value
Admission age (months) Median (IQR)	13 (51)	2 (1)	**p < 0.001**
Weight z-score Median (IQR)	-1.45 (3.20)	- 2.42 (2.33)	p = 0.063
Main Admission Diagnosis n (%):			
Surgical	257/534 (48.1)	2/35 (5.7)	
A,P & D	85/534 (15.9)	0/35 (0)	**p < 0.001**
LRT	100/534 (18.7)	29/35 (82.9)	
Other medical	92/534 (17.2)	4/35 (11.4)	
Viral Infection n (%)	25/517 (4.8)	14/34 (41.2)	**p < 0.001**
PCP/CMV n (%):			
PCP only	2/532 (0.4)	13/35 (37.1)	
CMV only	1/532 (0.2)	2/35 (5.7)	**p < 0.001**
PCP+ CMV	0/532 (0)	10/35 (28.6)	
TB n (%)	8/531 (1.5)	6/35 (17.1)	**p < 0.001**
Ventilation mode n (%):			
CPAP	15/516 (2.9)	0/33 (0)	**p < 0.001**
IPPV	426/516 (82.6)	23/33 (69.7)	
HFOV	23/516 (4.5)	10/33 (30.3)	
ICU duration (days) Median (IQR)	3 (5)	9 (10)	**p < 0.001**
Ventilation length (days) Median (IQR)	2 (5)	7.5 (10)	**p < 0.001**
Died in ICU n (%)	120/529 (22.7)	14/35 (40)	**p = 0.02**

Table 2: Comparison of HIV Negative and HEU patients admitted to the PICU

	HIV Negative	HEU	p-value
Admission age (months) Median (IQR)	13 (51)	3 (6)	**p < 0.001**
Weight z-score Median (IQR)	-1.45 (3.20)	-2.71 (4.34)	**p = 0.001**
Main Admission Diagnosis n (%):			
Surgical	257/534 (48.1)	39/109 (35.8)	
A,P & D	85/534 (15.9)	2/109 (1.8)	**p < 0.001**
LRT	100/534 (18.7)	43/109 (39.4)	
Other medical	92/534 (17.2)	25/109 (22.9)	
Viral Infection n (%)	25/517 (4.8)	12/106 (11.3)	**p < 0.001**
PCP/CMV n (%):			
PCP only	2/532 (0.4)	5/109 (4.6)	
CMV only	1/532 (0.2)	2/109 (1.8)	**p < 0.001**
PCP+ CMV	0/532 (0)	2/109 (1.8)	
TB n (%)	8/531 (1.5)	4/109 (3.7)	p = 0.129
Ventilation mode n (%):			
CPAP	15/516 (2.9)	4/105 (3.8)	p = 0.163
IPPV	426/516 (82.6)	83/105 (79)	
HFOV	23/516 (4.5)	10/105 (9.5)	
ICU duration (days) Median (IQR)	3 (5)	4 (8)	p = 0.163
Ventilation length (days) Median (IQR)	2 (5)	3.5 (7)	p = 0.443
Died in ICU n (%)	120/529 (22.7)	33/109 (30.3)	p = 0.091

Table 3: Comparison of HEU and HIV Infected patients admitted to the PICU

	HEU	HIV Infected	p-value
Admission age (months) Median (IQR)	3 (6)	2 (1)	p = 1.00
Weight z-score Median (IQR)	-2.71 (4.34)	- 2.42 (2.33)	p = 1.00
Main Admission Diagnosis n (%):			
Surgical	39/109 (35.8)	2/35 (5.7)	
A,P & D	2/109 (1.8)	0/35 (0)	**p < 0.001**
LRT	43/109 (39.4)	29/35 (82.9)	
Other medical	25/109 (22.9)	4/35 (11.4)	
Viral Infection n (%)	12/106 (11.3)	14/34 (41.2)	**p < 0.001**
PCP/CMV n (%):			
PCP only	5/109 (4.6)	13/35 (37.1)	**p < 0.001**
CMV only	2/109 (1.8)	2/35 (5.7)	
PCP+ CMV	2/109 (1.8)	10/35 (28.6)	
TB n (%)	4/109 (3.7)	6/35 (17.1)	**p = 0.006**
Ventilation mode n (%):			
CPAP	4/105 (3.8)	0/33 (0)	**p = 0.009**
IPPV	83/105 (79)	23/33 (69.7)	
HFOV	10/105 (9.5)	10/33 (30.3)	
ICU duration (days) Median (IQR)	4 (8)	9 (10)	**p = 0.009**
Ventilation length (days) Median (IQR)	3.5 (7)	7.5 (10)	**p = 0.001**
Died in ICU n (%)	33/109 (30.3)	14/35 (40)	p = 0.286

HIV infected children tended to be younger on admission than HIV negative but not HEU children. HIV infected children were more likely to be admitted with a LRT condition and were more frequently diagnosed with opportunistic (PCP/CMV/TB) and viral infections than HIV negative and HEU children. HIV infected children had a worse outcome than HIV negative and HEU children requiring HFOV more often and being ventilated and admitted to PICU for longer. The mortality in HIV infected children (40%) was higher than the mortality in HIV negative children (22.7%) (p = 0.02). Although the mortality rate in HIV infected children was higher than in HEU (30.3%) this difference was not statistically significant (p = 0.286).

HEU children were younger and had a lower weight for age z- score than HIV negative children. HEU children were more likely to be admitted with LRT conditions and to be diagnosed with

PCP and CMV, however they did not have a higher incidence of TB compared to HIV negative children. HEU children had a similar outcome to HIV negative children, requiring a similar duration of ventilation and ICU admission. The difference in mortality between HEU and HIV negative children was not statistically significant (p=0.091).

COMPARISON BY HIV STATUS FOR CHILDREN ADMITTED WITH A MEDICAL DIAGNOSIS

The subsequent comparison of patients admitted with a medical condition (lower respiratory tract or other) showed 11.3% (33/293) of children were HIV positive. HIV exposed children made up 34.5% (101/293) of total medical admissions of which 67.3% (68/101) were HEU and 32.7% (33/101) were HIV infected. The comparison of demographics and outcomes are shown in Table 4.

Table 4: Comparison by HIV status in children admitted to PICU with Medical Conditions

	HIV Negative	**HEU**	**HIV infected**	**p-value**
Weight z-score Median (IQR)	-2.11 (3.13)	-2.37 (4.48)	-2.42 (2.33)	0.338
Age (months) Median (IQR)	5.5 (22)	3 (6)	2 (1)	**0.001**
Duration ventilation Median (IQR)	4 (6)	4 (7)	8 (10)	**0.001**
Duration ICU Median (IQR)	4 (7)	5 (9)	9 (10)	**0.001**
Died in ICU (%)	62/190 (32.6)	27/68 (39.7)	14/33 (42.4)	0.387

When looking at the differences between the individual groups we found that HIV infected and HEU children were significantly younger on admission compared to HIV negative children ($p = 0.013$ and $p = 0.02$). PCP and CMV were more common in the HIV infected ($p < 0.001$) and HEU groups ($p < 0.001$) than the HIV negative group while TB was only more common in HIV

positive children ($p < 0.001$). HIV infected children required HFOV significantly more often than HIV negative children ($p = 0.04$). They also required longer ventilation ($p = 0.001$ and $p = 0.002$) and ICU stay ($p = 0.001$ and $p = 0.013$) than both HIV negative and HEU children. Although HIV infected and HEU children had a higher mortality this difference was not significant ($p = 0.387$).

DISCUSSION

This study reviewed the impact of HIV on outcomes in PICU. Despite an aggressive PMTCT programme and widely available ART, our study showed that HIV infected children made up 5.2% of the total admissions and 11.3% of medical admissions in the PICU. Previous South African studies showed similar proportions, with 10-12% of medical PICU admissions being HIV infected children (10, 11).

Since the introduction of expanded PMTCT programmes in South Africa fewer HIV exposed children are sero-converting and becoming HIV infected. This is evidenced in our study as only 32.7% of HIV exposed children admitted with a medical diagnosis had a positive PCR (i.e. confirmed to be HIV infected). Between 2003 and 2009 this figure was much higher with more than 80% of HIV exposed children admitted to the PICU being confirmed as being HIV infected (7, 14). With continually improved PMTCT programmes PICU should hopefully see a further decrease in the number of HIV infected children requiring admission. Every HIV infected case should be used as an opportunity to try and identify gaps in the PMTCT programme.

HEU and HIV infected children required admission to PICU at a younger age (two to three months) than HIV negative children. This was similar to local and international studies which showed most HIV infected children were younger than six months when admitted to PICU (4,

11, 14, 22). The younger age of admission is postulated to be due to the disease spectrum and severity in these groups. HIV infected children often present to a healthcare facility for the first time at this age with acute severe disease which may require PICU care (5). The younger age of admission shows that this age group of children are an important group to target for prevention of infectious diseases.

Furthermore, our study showed that HEU and HIV infected children were more likely to be admitted with LRT conditions than HIV negative children. This is similar to other studies which have shown up to 90% of HIV infected children are admitted to PICU with a LRT infection (9, 22, 23). The increased risk for LRT conditions in HIV exposed children is postulated to be related to the effect of HIV in-utero on the development of the immune systems, decreased maternal antibodies, increased exposure to household infections and even bone marrow suppression due to ART (16, 24).

Despite the routine use of trimethoprim-sulfamethoxazole prophylaxis in HEU and HIV infected infants, pneumocystis pneumonia remained an important cause of disease in the HEU and HIV infected children in our study. Pneumocystis pneumonia or pneumocystis and CMV co-infection occurred in 65.7% of HIV infected and 6.4% of HEU children in our study. Although treating HIV exposed patients for PCP and CMV has been shown to improve mortality, PCP still has a mortality of up to 44% despite the use of high dose trimethoprim-sulfamethoxazole, steroids and PICU admission (13-15). Co-infection with CMV further increases mortality despite the use of ganciclovir (14). The high incidence of pneumocystis in our sample was concerning and reflects poor implementation of trimethoprim-sulfamethoxazole prophylaxis. The high incidence of pneumocystis pneumonia and CMV most likely contributed significantly to the mortality in our patients.

HIV infected children tended to be admitted with more severe disease as reflected by their increased need for HFOV. In our PICU HFOV is only used in patients in whom adequate oxygenation and ventilation is not achieved with IPPV; the use of HFOV thus reflects disease severity. Despite having more severe disease HIV infected children did not have an increased need for inotropes, this is likely due to the primary respiratory pathology in the HIV infected children.

HIV infected children also required longer admission and ventilation than HEU and HIV negative children. Similar findings were noted in previous studies at our and other South African sites (10, 11, 23). The longer duration of ventilation and PICU stay are important as it impacts on already constrained resources and limited PICU beds. The longer PICU stay may also affect long-term outcomes such as mortality, morbidity from chronic lung disease and neurodevelopment (4, 22). The increased length of ventilation and PICU stay could be related to the severity of disease at presentation as well as the underlying immunocompromised state which may put these children at increased risk for nosocomial infections. Further studies are needed on the outcomes of HIV infected children once discharged form PICU with longer follow-ups.

While HIV infected children had a higher mortality than HEU and HIV negative children this difference was not significant in children admitted with a medical condition. The higher mortality in HIV infected children overall (including surgical and trauma conditions) can be explained by most HIV infected children being admitted with medical conditions. Medical conditions tend to have a worse outcome than patients admitted to PICU for post-operative care (25). The finding that HIV infection does not significantly affect mortality in PICU is supported

by other South African studies and is one of the main reasons why HIV infection is no longer an exclusion diagnosis for PICU admission (10, 11, 14).

Our HIV infected children had a mortality of 40% during the study period. This is higher than several studies done in Cape Town and Pretoria. A study from 2015 to 2017 by Ballot et al found that the higher mortality at our unit was possibly due to the unit admitting more severely ill children as the predicted mortality using the Paediatric Index of Mortality 3(PIM3) score was similar to the actual mortality (25). Reasons for this higher mortality can also be attributed to almost all the children in our unit being intubated and ventilated (92%) whereas other centres may admit more children to PICU not requiring invasive ventilation (10). The availability of high flow nasal prong oxygen in our general paediatric wards for LRT conditions has likely decreased the need for invasive ventilation in PICU and led to only the most severely ill children with LRT conditions being admitted to PICU. The high incidence of pneumocystis pneumonia and CMV in our centre also contributes to the higher mortality.

HEU children made up a significant percentage of PICU admissions. The number might in fact be higher as often HIV exposure in surgical patients is not well documented. This number is likely to rise with improved PMTCT. HEU were admitted at a younger age and had a lower weight-for-age z-score than HIV negative children. This shows that HEU children are at risk for malnutrition and severe disease at a young age and special attention should be given to these children when monitoring their growth and nutrition.

Although HEU children had similar outcomes to their HIV negative counterparts they seemed to have a higher burden of LRT conditions as well as opportunistic infections such as pneumocystis pneumonia and CMV. Numerous postulates have been made for this including

immune dysregulation in HEU children (14). The higher incidence of pneumocystis in these children shows that there is an opportunity to improve the implementation of trimethoprim-sulfamethoxazole prophylaxis in HEU children. Kitchin *et al* found that HEU children in their unit were often not on prophylaxis as the mothers were not aware of HIV exposure (14). Further studies are needed to establish why HEU children are presenting to PICU at a younger age and on interventions to decrease the risk of acute severe disease in this population which would decrease the pressure on PICU beds.

LIMITATIONS

The major limitation of our study was that it was a retrospective study of an existing database and not all data were complete. In classifying disease there was no specific definition used for PCP, rather it was a diagnosis made by the treating team based on clinical grounds supported by investigations. Another major limitation was that we did not have information on the timing of HIV diagnosis, maternal HIV history and PMTCT received by the mother and child which could help identify gaps in the PMTCT programme. Lastly, we did not have data on the long-term outcomes of patients.

CONCLUSION

In conclusion our study showed that HIV infected and HEU children presented to ICU at a younger age and were at increased risk for lower respiratory tract conditions than HIV negative children. The high incidence of PCP suggests the need to improve the implementation of PCP prophylaxis in HEU and HIV infected children. HIV infected children tend to have more severe disease requiring longer ventilation and PICU stay. They also have an increased mortality, but this difference was not significant in children admitted with medical conditions only. This supports that HIV infection on its own should no longer exclude a child from PICU admission.

379 HEU children had similar outcomes to HIV negative children. Further studies are needed to
380 identify gaps in PMTCT and PCP prophylaxis in HIV infected and HEU children as well as the
381 long-term outcomes of HIV infected and HEU children admitted to PICU.
382

LIST OF ABBREVIATIONS

A,D & P	Accidents, drownings and poisonings
ART	Antiretroviral Therapy
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
CPAP	Continuous Positive Airway Pressure
ELISA	Enzyme-Linked Immunosorbent Assay
HEU	HIV Exposed Uninfected
HFOV	High Frequency Oscillatory Ventilation
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IPPV	Intermittent Positive Pressure Ventilation
IQR	Interquartile Range
LDH	Lactate Dehydrogenase
LMICs	Low and Middle Income Countries
LRT	Lower Respiratory Tract
PCR	Polymerase Chain Reaction
PICU	Paediatric Intensive Care Unit
PIM3	Paeditric Index of Mortality 3
PJP	Pneumocystis jirovicii Pneumonia
PMTCT	Prevention of Mother to Child Transmission
REDCap	Research Electronic Data Capture
SPSS	Statistical Programme for the Social Sciences
WHO	World Health Organization

DECLARATIONS

Ethics Approval

The Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate M200436) as well as the clinical manager at CMJAH approved the study. Due to the retrospective nature of the study no informed consent was obtained.

Consent for Publication

Not applicable (article contains no data from any individual person).

Availability of data and materials

The datasets collected and analysed during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this study.

Authors Contribution

KW designed the study, analyzed the data, drafted the initial manuscript and was responsible for the final editing. DB supervised the study and reviewed the manuscript. All authors approved the final manuscript.

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APPENDIX A: RESEARCH PROTOCOL

A RETROSPECTIVE OBSERVATIONAL STUDY OF THE IMPACT OF HIV STATUS ON THE OUTCOME OF PAEDIATRIC INTENSIVE CARE UNIT ADMISSIONS

INTRODUCTION

Human Immunodeficiency Virus (HIV) remains an important healthcare problem worldwide affecting an estimated 1.7 million children (1). South Africa reported its first case of HIV in 1982 and reached the peak of the epidemic in 2003 leading to an increase in under-5 mortality to 78.1 per 1000 live births (2, 3). Since the introduction of Prevention of Mother to Child Transmission (PMTCT) programmes and access to Antiretroviral Therapy (ART) the statistics have improved but it is estimated that HIV still accounts for 1.2 – 8.7% of under-5 deaths (2).

Prior to the introduction of PMTCT it was estimated that 15-45% of HIV exposed infants would become HIV infected (4). With the introduction of expanded PMTCT programmes and the Universal Test and Treat strategy in 2016 (in which all persons testing positive for HIV qualify to start ART), South Africa has reduced its mother to child transmission rate to 0.9 – 3%, however postnatal acquisition of HIV is currently still a challenge (5-7).

Currently it is estimated that 260 000 children are HIV infected in South Africa with a further 3.5 million being HIV exposed but uninfected. Only 63% of HIV infected children in South Africa are currently on ART (8). HIV infected children not yet on treatment often present to a healthcare facility with an acute severe illness as their first presentation (3, 7). This places a significant demand on healthcare with a number of these children requiring admission to a Paediatric Intensive Care Unit (PICU) (7).

Prior to the availability of PMTCT and ART, HIV caused a rapid rise in hospital admissions with Chris Hani Baragwanath Hospital seeing an increase in admissions by 23.6% between 1992 and 1997

(9). The HIV related in-hospital deaths increased to 46% with the majority of these being caused by pneumonia (10). Other important causes of death in HIV infected children included gastroenteritis, septicaemia and meningitis (10). At this stage the acceptance of HIV infected children into PICU was controversial (11, 12).

Several studies demonstrated the poor outcomes of HIV infected children admitted to PICU with a mortality rate as high as 86 - 100% (11, 13). The majority of HIV infected children were admitted to PICU for respiratory failure (76%) and these respiratory illnesses were attributed to a wide range of causes with mixed infections (viral, bacterial and fungal) with multiple organisms occurring commonly (11, 13, 14). Furthermore a study at King Edward and Ngwelezana Hospitals showed that providing ventilation to HIV infected children did not improve their outcomes (13). Thus, prior to ART providing PICU care to HIV infected children was considered futile with minimal treatment options and little hope of cure (15).

As the HIV epidemic evolved and ART became available outcomes slowly started improving: a UK study over a 10-year period showed a mortality of 38% in HIV infected children admitted to PICU. They found that in those that survived 80% had good outcomes (16). In 2008 it was found that even though the mortality of HIV infected children admitted to PICU remained high at 34.7% ART had a protective effect and seemed to improve mortality (17).

Since the rollout of ART in South Africa short and medium term outcomes in HIV infected children have improved and HIV is no longer a reason to deny a child admission to PICU (3, 7, 18). With improved access to ART and improved treatment and ventilation strategies for opportunistic infections such as pneumocystis and cytomegalovirus mortality seems to have improved (3, 7). Several studies report no significant difference in mortality between HIV infected and HIV negative children, however there may be a difference in terms of duration of ventilation required (19, 20).

PICU is a limited resource in South Africa with only 23% of public hospitals having ICU or high care beds (21, 22). In 2008 there were only 1 186 ICU beds available in public with only 19.6% of these

beds allocated to neonatal and paediatric patients (21, 22). Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a tertiary hospital. The hospital provides healthcare to the Gauteng population as well as some of the neighbouring provinces and countries where tertiary services aren't readily available. CMJAH currently has 14 shared neonatal and PICU beds which are in high demand by both medical and surgical specialities. Usually only children requiring invasive ventilation are admitted. An audit of the CMJAH PICU in 2013 showed that 34% of patients admitted to the PICU were HIV exposed and 12% were HIV infected (20).

Many ethical dilemmas arise regarding which patients to accept to PICU in view of it being a limited resource. Many different ethical approaches have been suggested to deal with the allocation of PICU beds but currently there are no national guidelines on allocation of PICU beds (15, 23). Hospitals draw on international guidelines by the Royal College of Paediatrics and Child Health to help them decide which patients to accept to PICU (15, 23). These guidelines state that withholding or withdrawing care is acceptable in certain circumstances such as brain death, persistent vegetative states, no-hope situations, no purpose situations or unbearable situations (23). Hospitals such as the Red Cross War Memorial Children's Hospital have set up PICU admission policies in which children are excluded from PICU if the care is deemed to be futile, there is an underlying lethal condition or the outcomes for the condition are currently poor (15). Despite these policies bed occupancy remains high at 97% (15, 23).

Ballot et al (2019) further points out that the right of the child to basic healthcare and acting in a child's best interests has limited benefit when deciding who to admit to PICU, as severely constrained resources are in conflict with this (23). The need for low and middle income countries (LMICs) to develop their own critical care guidelines is clear (23). These should be based on available resources and disease spectrum, and in addition be guided by the local context such as ethics of caring and ubuntu (23).

The quality of care in PICU can be monitored by comparing actual mortality to predicted mortality using scoring systems such as the Paediatric Index of Mortality 3 (PIM3) (24). The PIM3 uses parameters collected within the first hour of admission to PICU to predict risk of death, the tool has previously been validated for use in South Africa (24, 25). The PIM3 can also be indirectly used as a marker to indicate the severity of illness in children admitted to PICU. Mortality rate in PICU can further be used to guide resource allocation (26).

Accepting children infected with HIV to PICU has created several new challenges. These challenges relate to providing adequate post-test counselling to parents of a critically ill child, deciding on when to start ART and managing the specific illnesses associated with HIV (3, 7). A study in Cape Town suggested that ART can be initiated rapidly even in PICU and that this may have contributed to the low mortality (13%) of HIV infected children admitted to PICU in this site (18).

Another challenge is the multi-organ involvement and severity of illness in HIV infected children. The most common reason for HIV infected children being admitted to PICU is an acute respiratory infection but other illnesses include pneumococcal sepsis, gastroenteritis, tuberculosis, haematological abnormalities and cytomegalovirus enteritis (which can be complicated by intestinal perforation) (3).

Important causative agents for respiratory failure in HIV infected children include pneumocystis and cytomegalovirus (CMV) (17, 27). Pneumocystis pneumonia (PCP) has been found to affect 38% of HIV infected children admitted to PICU and can also cause disease in HIV exposed uninfected children (27, 28). PCP has been found to negatively impact the outcome of HIV infected children with a mortality of 39 - 44% despite empiric treatment for PCP (17, 28). PCP coinfection with CMV further negatively impacts mortality with a mortality as high as 50% reported in HIV infected children with both PCP and CMV (27). In view of the above it is important to consider empiric treatment with trimethoprim-sulfamethoxazole and steroids for PCP in HIV infected children admitted with

pneumonia to PICU as well as ganciclovir for CMV (27). Despite the availability of these treatments the mortality from PCP and CMV remains high (27).

An important emerging population in PICU is the group of children who are HIV exposed but uninfected. Recent studies have shown that being HIV exposed is one of the strongest risk factors for pneumonia with up to 32% of children admitted to PICU with a severe lower respiratory tract infection (LRTI) being HIV exposed (19, 29). This increased risk for LRTIs may be related to the effect of HIV in-utero on the development of innate and adaptive immune systems , decreased maternal antibodies providing protection, increased exposure in the household to infectious disease and even bone marrow suppression due to ART (29, 30). It has also been shown that even though HIV exposure does not increase mortality in PICU these patients have a significantly longer hospital stay (19).

The PMTCT programme in South Africa has undergone several changes over the years and since 2013 all HIV infected pregnant women have qualified for lifelong ART (31). The improved implementation of the PMTCT programmes as well as the introduction of Universal Test and Treat policy in 2016 has allowed mother to child transmissions to drop to an all-time low (31). This in return leads to a greater population of HIV exposed uninfected children (29). This population of HIV exposed uninfected children is likely to become more important in a PICU setting. It is also important to note that since the expansion of PMTCT more children are infected postnatally likely through breastfeeding in undiagnosed mothers, this reveals an important gap in the PMTCT programme (4, 5)

Most recent mortality figures on HIV infected children admitted to PICU are still conflicting with reports ranging from 11 - 31.3% depending on the centre (18-20). Despite improved access to ART 14% of HIV infected infants die before 12 months of age (6). This reflects that HIV infected children have a need for PICU after the introduction of universal access to ART.

Further studies are needed to ascertain how HIV infection and exposure impacts on mortality, length of ventilation and length of stay in PICU as well as studies into the factors that predict their outcomes. This will allow more PICU resources to be motivated for and will assist with drawing up guidelines

on which children to accept to PICU. Further studies are also needed to determine the unique healthcare needs of HIV exposed children in PICU. This has led to an important research question: "Do HIV infected and HIV exposed uninfected children have a worse outcome than HIV unexposed children in PICU?"

AIM

To compare the characteristics and outcomes of HIV infected, HIV exposed uninfected and HIV unexposed children admitted to a PICU at a tertiary hospital in Johannesburg, after the introduction of expanded PMTCT programmes and universal access to ART.

OBJECTIVES

1) To determine the proportion of children (excluding neonates) who are HIV infected, HIV exposed uninfected and HIV unexposed in PICU.
2) To describe and compare the demographics, disease profile and treatment of HIV infected, HIV exposed uninfected and HIV unexposed children in PICU.
3) To compare the length of stay and the mortality of HIV infected, HIV exposed uninfected and HIV unexposed children in PICU.

METHODS

Study Design

This study is a retrospective, observational study comparing HIV infected, HIV exposed uninfected and HIV unexposed children admitted to PICU.

Study Population

Children admitted to the PICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from January 2015 to December 2019.

Inclusion Criteria

- Male and female children who are between 29 days and 12 years.
- Children in whom the HIV status is known.

Exclusion Criteria

Children with missing records and/or missing HIV results will be excluded.

Sample Size

Extrapolating from an audit of PICU admissions at CMJAH from 2013-2014 it is estimated that the study will have a sample size of 1 200 of which it is estimated that 140 will be HIV infected and 400 HIV exposed uninfected (20).

Study Procedure

Permission will be obtained from the chief executive officer (CEO) (see appendix A) and head of the paediatrics at CMJAH (see appendix B) to access the information of patients who were admitted to PICU during the study period. Ethical approval will be obtained from the University of Witwatersrand Human Research Ethics Committee.

Secondary analysis of an existing database will be performed. This database is created through data collected on discharge from PICU for the purpose of quality improvement. The data is verified at several different points during collection and is managed using the Research Electronic Data Capture (REDCap) system hosted by the University of the Witwatersrand (32).

De-identified data will be retrieved from the database for the study period with permission from the administrator of the database (see appendix C). This data will contain no names, no hospital numbers and no dates. Each participant will be allocated a study number and the data will be collected into a

data sheet with no patient identifiers to maintain patient confidentiality. This data will then be entered into an Excel spreadsheet for analysis.

At all times the data retrieved will be stored safely and securely and will not contain any patient identifiers. No patient records will be removed from the hospital premises.

Data Collection

A data collection sheet (see appendix D) will be used to collect the data for each participant.

The following information will be collected (see appendix D for full details):

- Demographics:
    - Age and gender
    - Weight and height classified according to z-scores (33)
- Diagnosis
- Length of ICU stay and death in ICU
- HIV status: infected, exposed, unexposed including CD4 count if infected
- Mechanism and duration of ventilation
- Ionotropic support
- Cardiac arrest during or prior admission
- PIM3 scores: admission parameters used to determine PIM3 score
- Bacterial, fungal or viral sepsis
- CMV viral load
- Treatment for PCP or CMV

Data will then be entered onto an Excel spreadsheet for interpretation and analysis.

Data Analysis

The sample will be described using frequencies and percentages for categorical variables. Continuous variables will be described using means with standard deviations for data with a normal distribution and medians with interquartile ranges for skewed data.

The sample will then be divided into three groups by HIV status, namely: HIV infected, HIV exposed uninfected and HIV unexposed. These groups will be compared using Chi-square tests for categorical variables. Continuous variables will be compared using ANOVA for data with a normal distribution and non-parametric tests for skewed data.

ETHICAL CONSIDERATIONS

Risks to Patients

This study deals with confidential information about patients' HIV status. There is no risk to this confidentiality being lost as only de-identified data will be used. None of the data collected will contain patient identifiers such as name, hospital number, dates of birth or dates of admission (refer to methods) and data will be securely stored.

Benefits to Patients

Patients will not receive any direct benefit from being involved in the study.

Informed Consent

As this is a retrospective study informed consent will not be obtained. However patient information will be kept anonymous. Data will be stored securely.

Study Costs

There will be no costs incurred to study participants and no reimbursement.

Costs involved include costs of photocopying and printing which is estimated at R1000.

LIMITATONS

This is a retrospective study therefore it relies on the accuracy of patient records as well as the data capturing of this information by third parties. A major limitation might be that not all information was available or captured for the study population.

Another limitation is that the populations in each group, namely HIV infected, HIV exposed uninfected and HIV unexposed might not be completely homogenous. This means that there could be confounding variables that could make comparison of the groups difficult.

TIMELINE

	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Literarture review																						
Preparing protocol																						
Protocol assessment																						
Ethics application																						
Collecting data																						
Data Analysis																						
Writing up – thesis																						
Submission and marking																						

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APPENDIX B: AUTHOR GUIDELINES FOR BMC PEDIATRICS

BMC Pediatrics

Research article

Criteria

Research articles should report on original primary research, or present a new experimental or computational method, test or procedure. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a completed CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered. Studies reporting descriptive results from a single institution or region will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

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BMC Pediatrics strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

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Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:

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    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
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- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
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- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
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Please see below for details on the information to be included in these sections.

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Manuscripts reporting studies involving human participants, human data or human tissue must:

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- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

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- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
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University site

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- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
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APPENDIX C: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr K Whitehead

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200436

NAME: (Principal Investigator)	Dr K Whitehead
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*A retrospective observational study of the impact of HIV status on the outcome of paediatric intensive care unit admissions* ***Change of study title noted on 2021/06/15***
DATE CONSIDERED:	2020/04/24
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor D Ballot
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/04/24

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **April** and therefore reports and re-certification will be due in the month of **April** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Whitehead — 23/06/2021

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FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

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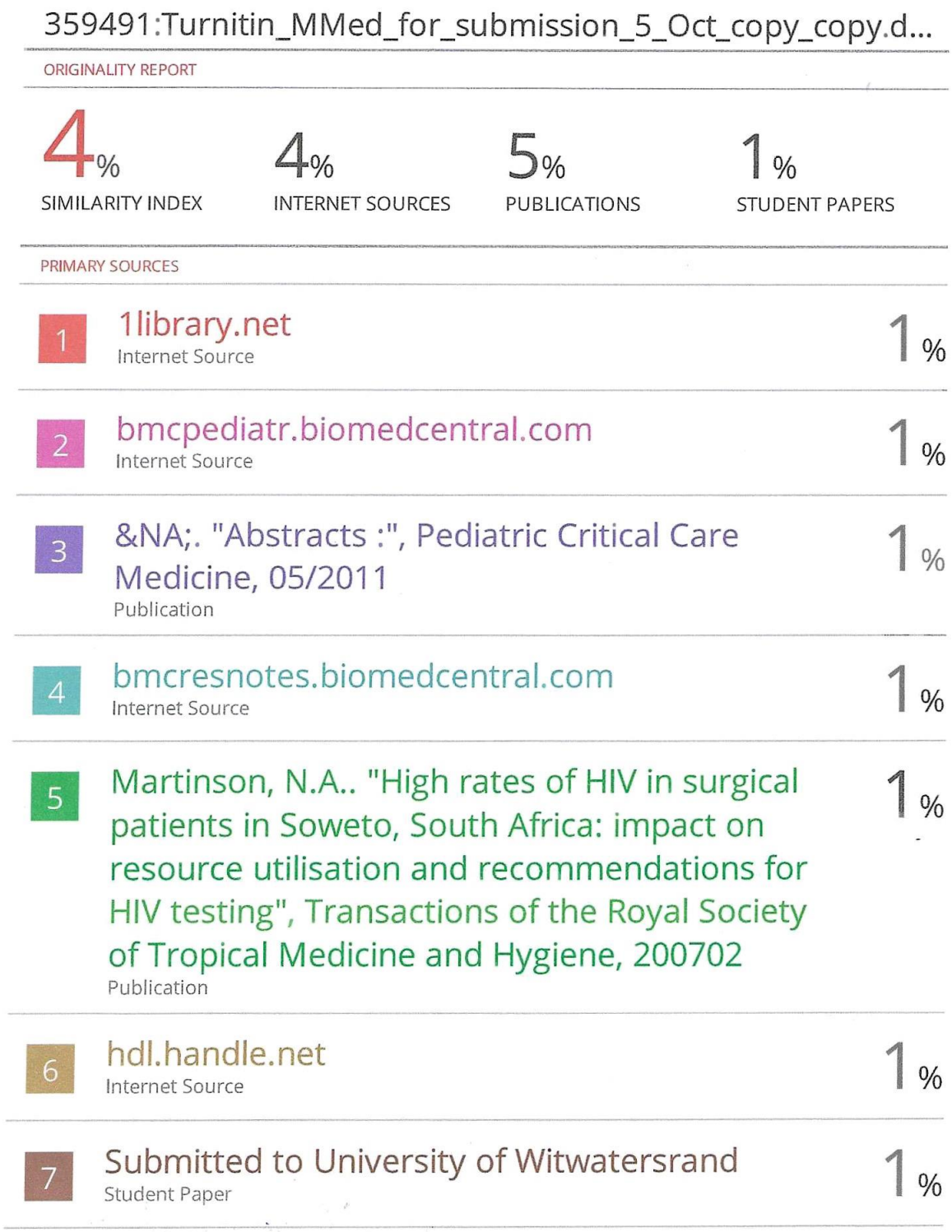
I KIM WHITEHEAD (Student number: 359491) am a student registered for the degree of MMed in Paediatrics in the academic year 2022.

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