AN AUDIT OF HIV PATIENTS ADMITTED TO A MULTIDISCIPLINARY TERTIARY LEVEL INTENSIVE CARE UNIT

Dr Rammona W Maphula

Student No. 0504807J

A Research Report submitted to the Faculty of Health of the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Emergency Medicine

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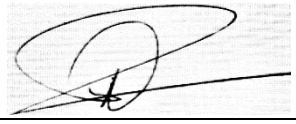
DECLARATION

I, Rammona W Maphula, hereby declare that this research report is my own work and has not been submitted or presented for any other degree or professional qualification at this or any other institution. This research was undertaken in the Division of Emergency Medicine, University of the Witwatersrand, Johannesburg.

Signature of Student:  Date: 17 / 12 / 2019

Name of Supervisor 1: Professor Abdullah E Laher

Signature of Supervisor 1:  Date: 17 / 12 / 2019

Name of Supervisor 2: Professor Guy Richards

Signature of Supervisor 2:  Date: 17 / 12 / 2019

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AUTHORS AND AFFILIATIONS

Rammona W MAPHULA[1]; MBChB; rwmaphula@gmail.com

Abdullah E LAHER [1,2]; MBBCh, MMed, FCEM, Cert Critical Care, EDIC, DipPEC, DCH, DipAllerg, DipHIVMan; abdullahlaher@msn.com

Guy A RICHARDS[2]; MBBCh, PhD, FCP, FRCP, FCCP; guy.richards@wits.ac.za

[1]Department of Emergency Medicine Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[2]Department of Critical Care, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

CORRESPONDING AUTHOR

Professor Abdullah E LAHER; Department of Emergency Medicine, Faculty of Health Sciences, University of Witwatersrand, 7 Jubilee Road, Parktown, Johannesburg, 2193, South Africa; Email abdullahlaher@msn.com; telephone: +27848402508

CONFLICTS OF INTEREST

The authors hereby certify that this submission is not under publication consideration elsewhere and is free of conflict of interest.

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R.W.M was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up and approval of the final manuscript. A.E.L assisted with the study design, data analysis, interpretation of results, preparation of the manuscript and approval of the final manuscript. G.R assisted with the study design, data analysis, interpretation of results, preparation of the manuscript and approval of the final manuscript.

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HIV, critical care, ICU, inotrope, mechanical ventilation, haemodialysis, CD4 cell count

SUBMISSION LETTER TO THE EDITOR

Dear Editor- "HIV Medicine"

Thank you for considering our manuscript entitled: *"**Patterns of presentation and survival of HIV infected patients admitted to a tertiary level ICU"***

South Africa is unique in that it has the largest number of people living with HIV, the majority of whom are dependent on public healthcare resources. There is limited data in developing countries on the outcomes of HIV infected patients admitted to the ICU. In addition to several differences to previous similar designed studies, we are the first to report on the Risk Adjusted Mortality Ratio (RAMR – observed ICU mortality rate divided by the predicted ICU mortality rate based on the APACHE II scoring tool) in HIV infected ICU patients.

We believe that our findings will provide significant insight into the presentation and outcome of HIV patients admitted to the ICU in a resource limited setting. We are certain that this manuscript will appeal to the readership of ***HIV Medicine.*** Furthermore, it carries a high citation potential, as critical care and HIV are relevant topics to almost all disciplines of medicine.

ABSTRACT

Background: South Africa has the largest number of people living with HIV. There is limited data in developing countries on the outcomes of HIV infected patients in the intensive care unit (ICU). The objectives of this study were to describe the pattern of presentation of these patients and to determine factors that may influence survival to ICU discharge.

Methods: Medical charts of 204 consecutive HIV infected individuals that were admitted to the Charlotte Maxeke Johannesburg Academic Hospital adult general ICU during the 2017 calendar year were retrospectively reviewed. Relevant data was subjected to univariate and multivariate analysis.

Results: Two-hundred and four (22.6%) out of a total of 903 patients that were admitted to the ICU were HIV positive. Sepsis related illnesses was the most common reason for ICU admission, (n=95, 46.6%), followed by post-operative care (n=69, 33.8%) and non-sepsis related illnesses (n=40, 19.6%). The median length of stay in the ICU was 5 (2-9) days. ICU mortality was 33.3% (n=68). On univariate analysis, age (p=0.039), length of stay in ICU (p=0.040), primary diagnostic category ($p<0.05$), sepsis acquired during ICU stay (p=0.012), requirement for inotropic/vasopressor support ($p<0.001$), requirement for mechanical ventilation ($p<0.001$), requirement for haemodialysis (p=0.001), CD4 cell count (p=0.011), APACHE II score ($P<0.001$) and SOFA score ($p<0.001$) were significantly associated with mortality.

Conclusion: Age, diagnostic category, sepsis acquired during ICU stay, inotrope/vasopressor administration, mechanical ventilation, haemodialysis, CD4 cell count, APACHE II score, SOFA score and length of ICU stay are associated with ICU mortality in HIV infected patients.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a global healthcare problem, with over 38.8 million infected individuals [1], 2 million new cases annually and 1.2 million deaths per year [2]. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS) 2016 estimates, Eastern and Southern Africa were the world's most affected regions, with an estimate of 19.4 million HIV infected people living with HIV in 2015 [3].

Approximately 5-10% of all hospitalized HIV infected patients require intensive care unit (ICU) admission, 40% of whom are only diagnosed with HIV after admission [4,5]. Half the number of patients with a known diagnosis of HIV have not been initiated on antiretroviral therapy (ART) at the time of ICU admission [5]. HIV related illnesses (e.g. opportunistic infections), complications of ART and HIV unrelated pathology such as trauma and post-operative care are some of reasons that these patients may require admission to the ICU [6,7].

With the increased availability of ART, there has been an improvement in the survival of HIV infected individuals [8,9]. Various studies have reported lower rates of HIV related ICU admissions since the introduction of ART [9,10]. Risk factors for poor short-term survival after ICU discharge were found to be similar in HIV positive and negative subjects. These included poor baseline health, higher severity of acute illness and delayed delivery of critical care [11]. In addition, a higher severity of illness score, low serum albumin, requirement for vasopressor or inotropic support, need for mechanical ventilation, PCP diagnosis and the presence of other AIDS-related illnesses have also been associated with poorer outcomes in patients with HIV [5,11,12]. Surprisingly, CD4 cell count and HIV viral load were not shown to predict ICU survival [5].

ART has been available at public health care facilities in South Africa since 2004 for patients with a CD4 cell count below 200 cell/mm^3 [13,14]. Since 2015 however, ART has been made accessible to all public sector patients irrespective of the CD4 cell count [15,16]. Data on the outcomes of HIV infected ICU patients in developing countries is limited. Due to the high burden of HIV in South Africa [3], coupled with resource limitations in the public healthcare setting [17], we hypothesized that ICU admission patterns and outcomes may be different to those in other settings. The objective of this study was to describe the pattern of presentation of these patients to the ICU and to determine factors that may influence survival to ICU discharge.

METHODS

Medical charts of 204 consecutive HIV infected individuals that were admitted to the adult general ICU of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 01 January 2017 until 31 December 2017 were retrospectively reviewed. CMJAH is a tertiary level hospital that is affiliated with the University of the Witwatersrand. The institution has 1088 beds with 6 distinct ICU wards, viz. neurosurgical ICU, cardiac ICU, cardiothoracic ICU, trauma ICU, paediatric ICU and adult general ICU. The adult general ICU has a capacity of 19 ICU beds. There are no set criteria governing patient admission with the decision to admit being left to the discretion of the ICU physician on call. However, the default is to admit all critically ill patients where possible, particularly those requiring mechanical ventilation, haemodialysis or inotropic/vasopressor support.

Prior to commencement of the study, the primary investigator underwent informal training on the methodology and principles of data collection from medical charts. Permission to conduct

the study was obtained from the CEO of the hospital as well as the Head of Department of the adult general ICU. Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Clearance certificate number M180346).

Medical charts of all patients admitted to the ICU over the stipulated data collection period were reviewed. After selecting the medical charts of patients with HIV infection, relevant data was extracted by the primary investigator. A standardised form was used to collect data that included patient demographics, diagnosis, reason for ICU admission, co-morbidities, sepsis acquired during ICU stay, requirement for inotrope/vasopressor support, mechanical ventilation, renal replacement therapy, surgical procedure performed during ICU admission, diagnosis of HIV after admission to ICU, use of ART, most recent CD4 cell count, most recent HIV viral load, serum albumin concentration and length of ICU stay. The Acute Physiology and Chronic Health Assessment (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score, ICU mortality, hospital mortality and the Risk Adjusted Mortality Ratio (RAMR – observed ICU mortality rate divided by the predicted ICU mortality rate based on the APACHE II scoring tool) were also determined. Where data was missing, medical charts and electronic laboratory results were rechecked. The process of data collection was periodically monitored by the study supervisors.

Inter-rater reliability was assessed via an independent individual with experience in methods of data collection. This individual was blinded to the study aims and objectives. A sample of 25 randomly selected medical charts were re-collected and compared to the data that was collected by the primary investigator.

Where indicated, mean and standard deviation (SD) or median and interquartile range (IQR) of various variables were reported. Where appropriate, the Student's t-test, Mann-Whitney rank sum test, Pearson's Chi squared test and the Fisher's exact test were used to compare sociodemographic details, primary diagnosis, ICU sepsis, requirement for inotropic/vasopressor support, mechanical ventilation, haemodialysis, surgical procedures performed during ICU stay, HIV diagnosed after ICU admission, ART initiation prior to ICU admission, HIV viral load, median CD4 cell count, median serum albumin level, median APACHE II score, median SOFA score and length of ICU stay between patients that survived and those that died. Using univariate logistic regression, the odds ratios (OR) for ICU mortality was determined for each variable. Factors showing a possible association (defined as a p-value of ≤ 0.1 on univariate analysis) were included as covariates in a multivariate logistic regression model. Non-significant factors were dropped with manual backward regression. A two-sided p-value of <0.05 was considered significant throughout. Analysis was carried out using Stata version 15 (StataCorp Limited, Texas, United States of America). Reporting of study findings were in conformance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [18]

RESULTS

A total of 903 patients were admitted to the ICU between 01 January 2017 and 31 December 2017. Of these, 204 (22.6%) were HIV positive and were included in the final sample for analysis. The mean age (SD) of HIV positive study patients was 40.0 (11.8) years, with the majority being female (n=121, 59.3%) and unemployed prior to hospital admission (n=137, 67.2%). ICU and hospital mortality amongst HIV positive subjects were 33.3% (n=68) and 16.7% (n=34) respectively.

Table 1 describes and compares diagnostic category, sepsis acquired during ICU stay, inotropic/vasopressor administration, mechanical ventilation, haemodialysis, surgical procedures performed during ICU admission, HIV diagnosed after ICU admission, ART initiation prior to ICU admission, HIV viral load, median CD4 cell count, median serum albumin concentration, median APACHE II score, median SOFA score and median length of ICU stay between HIV positive subjects that survived and those that died. Sepsis related illnesses were the most common reason for ICU admission, (n=95, 46.6%), followed by post-operative care (n=69, 33.8%) and non-sepsis related illnesses (n=40, 19.6%). Bacterial pneumonia (n=32, 33.7%) was the most common cause of sepsis. Other causes of sepsis / infection related admissions included pulmonary tuberculosis (n=15, 15.8%), pneumocystis jiroveci pneumonia (n=7, 7.4%), malaria (n=6, 6.3%), bacterial meningitis (n=4, (4.2%) and acute gastroenteritis (n=3, 3.2%). The source of sepsis was not identified in 19 (20.0%) patients. Sixteen (8.8%) patients acquired sepsis during their ICU admission. Of the 69 patients admitted for post-operative care, 32 (46.4%) underwent an elective procedure whilst 37 (53.6%) underwent emergency surgery. More than half the number of patients (n=114, 55.9%) required inotropic/vasopressor support, three-quarter (n=152, 74.5%) required mechanical ventilation, 81 (39.7%) required renal replacement therapy and 38 (18.6%) underwent surgery during their stay in ICU. The RAMR was 0.51. The median length of stay in the ICU was 5 (2-9) days.

Table 1: Characteristics of study subjects

Characteristics	**Entire cohort (n=204)**	**Survived (n=136)**	**Died (n=68)**	**OR (95% CI)**	**P-value**
Mean age in years (SD)	40.0 ± 11.8	38.8 ± 11.0	42.5 ± 13.2	1.03 (1.00-1.05)	**0.039**
Sex					0.920
Female	121 (59.3)	81 (59.6)	40 (58.8)	1.00 (Reference)	
Male	83 (40.7)	55 (40.4)	28 (41.2)	1.03 (0.57-1.86)	
Employment status					0.716
Employed	67 (32.8)	44 (32.4)	23 (33.8)	1.00 (Reference)	
Unemployed	137 (67.2)	92 (67.6)	45 (66.2)	1.12 (0.60-2.11)	
Primary diagnostic category					
Post-operative care	69 (33.8)	56 (41.2)	13 (19.1)	1.00 (Reference)	**0.005**
Non-sepsis related illness	40 (19.6)	24 (17.6)	16 (23.5)	2.87 (1.20-6.88)	**0.018**
Sepsis/infection related illness	95 (46.6)	56 (41.2)	39 (23.5)	3.05 (1.47-6.34)	**0.003**
Sepsis acquired during ICU stay	16 (8.8)	6 (4.4)	10 (14.9)	3.80 (1.32-11.0)	**0.012**
Inotrope/vasopressor administered	114 (55.9)	52 (38.5)	62 (91.2)	16.5 (6.7-40.9)	**<0.001**
Mechanical ventilation	152 (74.5)	87 (64.0)	65 (95.6)	12.2(3.6-40.9)	**<0.001**
Haemodialysis	81 (39.7)	43 (31.6)	38 (55.9)	2.74 (1.5- 5.0)	**0.001**
Surgical procedure performed during ICU admission	38 (18.6)	24 (17.6)	14 (20.6)	1.21 (0.58-2.52)	0.613
HIV diagnosed after ICU admission	44 (21.5)	26 (19.1)	18 (26.5)	1.52 (0.77-3.02)	0.234
ART initiated prior to ICU admission	142 (69.6)	97 (71.3)	45 (66.2)	0.96 (0.46-2.00)	0.915
HIV viral load (copies/mL)					
Undetectable	28 (28.0)	22 (33.3)	6 (17.7)	1.00 (Reference)	0.220
0-1000	38 (38.0)	22 (33.3)	16 (47.1)	2.67 (0.88-8.08)	
1001-10 000	4 (4.0)	4 (4.0)	0 (0.0)	N/A	
10 001-100 000	13 (13.0)	9 (13.6)	4 (11.8)	1.63 (0.37-719)	
>100 000	17 (17.0)	9 (13.6)	8 (23.5)	3.26 (0.88-12.10)	
Median CD4 cell count (IQR)	148 (55-323)	197.5 (85-357)	88 (41-209)	0.99 (0.99-1.00)	**0.011**
Median serum albumin (g/L) (IQR)	24 (20-29)	24 (19-29)	24 (21-30)	1.02 (0.96-1.09)	0.454
Median APACHE II score (IQR)	22 (15-29)	18 (14-24)	27 (22-34)	1.11 (1.07-1.15)	**<0.001**
Median SOFA score (IQR)	8 (4-12)	6 (3-10)	12 (9-14)	1.27 (1.17-1.38)	**<0.001**
Median length of stay in days (IQR)	5 (2-9)	5 (3-9)	4 (2-11)	1.03 (1.00-1.06)	**0.040**

IQR=Interquartile Range; ICU=Intensive Care Unit; ART=Anti-Retroviral Therapy; APACHE=Acute Physiology and Chronic Health Evaluation; SOFA=Sequential Organ Failure Assessment

The relationship between ICU mortality and the APACHE II score and between ICU mortality and the SOFA score amongst HIV positive subjects is described in figures 1 and 2 respectively. Table 2 compares ICU mortality between HIV positive and HIV negative patients. The overall ICU mortality was significantly higher (p=0.00001) amongst HIV positive patients (n=68, 33.3%) compared to HIV negative patients (n=131, 18.7%). Although HIV positive patients with a non-sepsis related illness had a significantly higher ICU mortality rate than HIV negative

patients (40.0% vs 21.8%, p=0.013), there were no statistically significant differences in ICU mortality between HIV positive and HIV negative patients that were admitted to the ICU for either post-operative care (p=0.132) or for a sepsis/infection related illness (p=0.130).

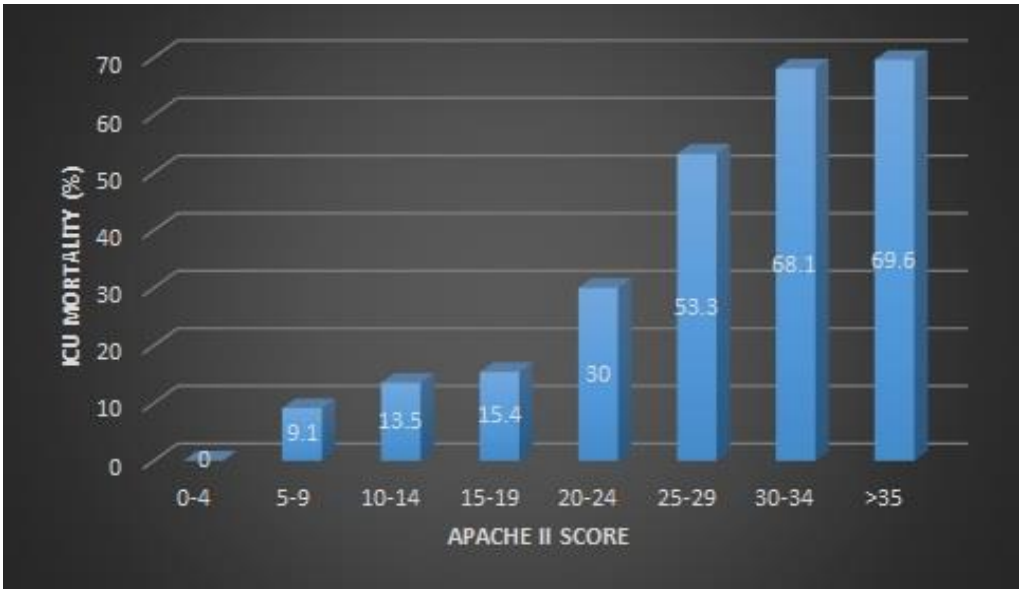

Figure 1: Distribution of APACHE II score amongst the study cohort and its relationship with ICU mortality

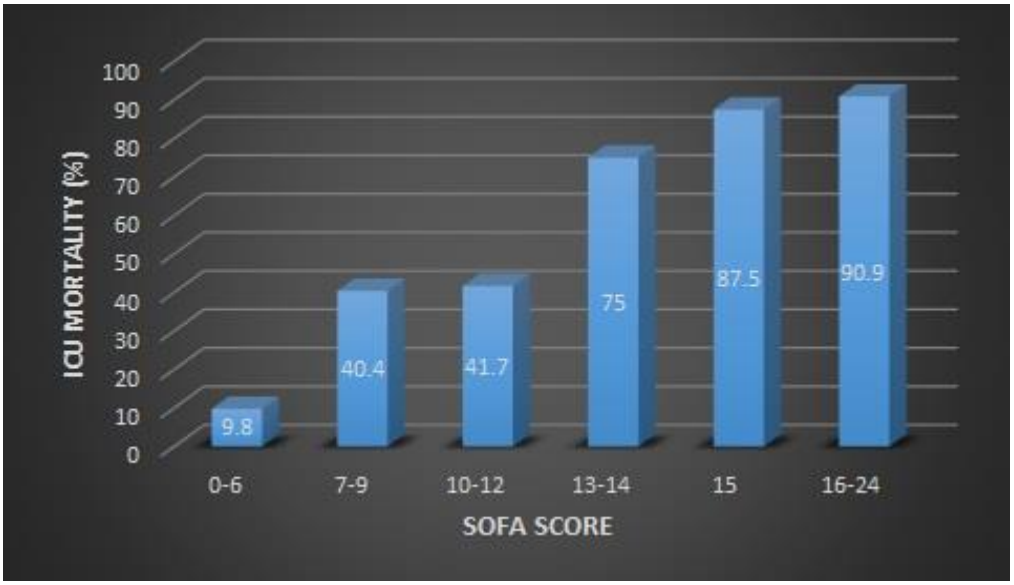

Figure 2: Distribution of SOFA score amongst the study cohort and its relationship with ICU mortality

Table 2: Comparison of ICU mortality between HIV positive and HIV negative patients

Primary diagnostic category	ICU mortality amongst HIV positive patients	ICU mortality amongst HIV negative patients	P-value
Post-operative care	13/69 (18.8%)	40/331 (12.1%)	0.132
Non-sepsis related illness	16/40 (40.0%)	55/252 (21.8%)	**0.013**
Sepsis/infection related illness	39/95 (41.1%)	36/116 (31.0%)	0.130
Overall	*68/204 (33.3%)*	*131/699 (18.7%)*	***0.00001***

Multivariate analysis of significant parameters emanating from univariate analysis of the data (table 3) revealed that a non-sepsis related diagnosis (p=0.030), requirement for inotropic/vasopressor support (p=0.009) and mechanical ventilation (p=0.037) were significantly associated with ICU mortality.

Table 3: Multivariate analysis of significant parameters emanating from univariate analysis

Characteristics	**Univariate**	**P-value**	**Multivariate**	**P-value**
Mean age in years	1.03 (1.00-1.05)	0.039	1.01 (0.98-1.05)	0.484
Length of stay	1.03 (1.00-1.06)	0.040	1.00 (0.97-1.04)	0.958
Primary diagnostic category				
Post-operative care	1.00 (Reference)		1.00 (Reference)	
Non-sepsis related illness	2.87 (1.20-6.88)	0.018	3.59 (1.13-11.38)	**0.030**
Sepsis/infection related illness	3.05 (1.47-6.34)	0.003	2.41 (0.98-5.94)	0.055
Median CD4 cell count	0.99 (0.99-1.00)	0.011	0.99 (0.99-1.00)	0.080
APACHE II Score	1.11 (1.07-1.15)	<0.001	1.04 (0.99-1.09)	0.124
SOFA score	1.27 (1.17-1.38)	<0.001	1.08 (0.99-1.18)	0.075
Sepsis acquired during ICU stay	3.80 (1.32-11.00)	0.012	2.51 (0.64-9.76)	0.051
Inotrope/vasopressor administered	16.50 (6.70-40.90)	0.001	4.51 (1.45-14.03)	**0.009**
Mechanical ventilation	12.20(3.60-40.90)	0.001	4.48 (1.10-18.33)	**0.037**
Haemodialysis	2.74 (1.50- 5.00)	0.001	0.90 (0.38-2.13)	0.804

Factors associated with ICU mortality on univariate analysis of the data included mean age (p=0.039), the primary diagnostic category (p<0.05), sepsis acquired during ICU stay (p=0.012), requirement for inotropic /vasopressor support (p<0.001), mechanical ventilation (p<0.001), haemodialysis (p=0.001), median CD4 cell count (p=0.011), median APACHE II score (p<0.001), median SOFA score (p<0.001) and median length of ICU stay (p=0.040).

Of note, every year increase in age and every additional day spent in the ICU, were each associated with a 3% higher odds of dying (OR 1.03, 95% CI 1.00-1.05, p=0.039 and OR 1.03, 95% CI 1.00-1.06, p=0.040 respectively). Patients with sepsis (OR 3.05, 95% CI 1.47-6.34) and non-sepsis related (OR 2.87, 95% CI 1.20-6.88) diagnoses were more likely to die in ICU compared to those admitted for post-operative care (p=0.005). Those that acquired sepsis during their stay in ICU were almost 4 times more likely to die (OR 3.80, CI 1.32-11.0, p=0.012), while patients who required inotropic/vasopressor support, mechanical ventilation or haemodialysis were approximately 17 times (OR 16.5, CI 6.7-40.9, p<0.001), 12 times (OR 12.2, CI 3.6-40.9, p<0.001) and 3 times (OR 2.74, CI 1.5-5.0, p=0.001) more likely to die respectively. The higher the CD4 cell count, the less likely were patients to die during their stay in ICU (OR 0.99, CI 0.99-1.00, p=0.011). For every 1-unit increase in the APACHE II score at admission, there was a 11% increase in the likelihood of ICU mortality (OR 1.11, CI 1.07-1.15, p<0.001), while for every 1-unit increase in the SOFA score, there was a 27% increase in the likelihood of ICU mortality (OR 1.27, CI 1.17-1.38, p<0.001).

DISCUSSION

Although univariate analysis identified mean age, primary diagnostic category, sepsis acquired during ICU stay, requirement for inotropic/vasopressor support, mechanical ventilation, haemodialysis, median CD4 cell count, median APACHE II score, median SOFA score and median length of ICU stay as significant factors associated with poor ICU mortality, only a non-sepsis diagnosis, requirement for inotropic/vasopressor support and the requirement for mechanical ventilation were the major contributors to ICU mortality on multivariate analysis.

These findings are similar to other studies which also evaluated significant contributors to ICU survival/mortality [5,11,12].

Sepsis (46.6%) was the major reason for ICU admission, with lower respiratory tract infections (56.9%) being the major source. This finding is in keeping with results of previous studies that have also reported respiratory illnesses as being the common reason for ICU admission amongst HIV infected patients [19–21].

Despite the fact that that the overall ICU mortality rate was significantly higher amongst HIV positive compared to HIV negative patients in this study, it is noteworthy that approximately two-thirds of HIV positive patients did survive to ICU discharge and that there were no significant ICU mortality differences in the subsets of patients that were admitted to the ICU for post-operative care or sepsis/infection related illnesses. This is despite the large proportion of HIV positive study patients (82%) that had a detectable viral load. Similar to our findings, a study that compared the effects of HIV status on clinical outcomes of surgical sepsis in the KwaZulu-Natal province of South Africa, did not reported significant differences in clinical presentation, spectrum of surgical disease and morbidity/mortality [22]. Weledji et al. concluded that HIV/AIDS patients should not be regarded as a homogenous group and that the best predictor of peri-operative morbidity and mortality are scores that measure general health such as the American Society of Anesthesiologist (ASA) risk score [23]. Hence, clinicians should adopt a liberal threshold for admitting HIV positive patients to the ICU.

Unlike the findings of other studies [12,24], HIV positive patients from this study that died in ICU were significantly older than those that survived. Morris et al. for example, did not report

any differences with regards to age, sex, race, ethnicity or HIV risk factors between survivors and non-survivors [25]. In keeping with findings of Kwizera et al. [24], the median length of ICU stay was marginally but statistically significantly longer in those that survived to discharge from ICU. A plausible reason may be that HIV positive individuals who demise in ICU are more acutely ill upon ICU admission.

According to Kwizera et al., sepsis was not a significant contributor to mortality, however, according to Akgun et al, sepsis was a significant predictor of mortality and poorer outcomes [5,24]. In this study we found that patients admitted with sepsis (OR 3.05, CI 1.47-6.34) and those that acquired sepsis during their stay in ICU (OR 3.80, CI 1.32-11.0) were more likely to die, however, as per the multivariate analysis, only a non-sepsis related diagnosis was significantly associated with mortality (p=0.030). Similar to other studies, we also found that requirement for inotropic/vasopressor support, mechanical ventilation or haemodialysis were significantly associated with increased mortality [5,26,27].

In this study, patients who were already on ART prior to hospital admission appeared to be more likely to survive, however, the difference was not statistically significant (p=0.915). This is in contrast to Morris et al. who found that ART initiation prior to ICU admission significantly improved survival [25]. Although ART's were not initiated in any of the study patients during their stay in ICU, some studies have shown benefit [28] while others did not [26]. Mia et al. recommended that the decision to continue or initiate ART in the ICU should be individualised, depending on the underlying disease process [29].

In this study, a lower mean CD4 cell count was significantly associated with ICU mortality. Although mortality was highest amongst patients with a HIV viral load of >100 000 copies/mL (47.1%), the associations was not significant (p=0.220). Other studies did not show any association between the CD4 cell count or HIV viral load and ICU survival/mortality [25,30]. Subjects that were newly diagnosed with HIV after ICU admission made up a large proportion of patients in whom the HIV viral load was measured (44 out of 100 patients). This is a likely reason for the low proportion of patients (28%) in whom the HIV viral load was undetectable. Poor ART compliance and ART resistance are other possible factors that may have contributed to this low figure [31].

With regards to serum albumin concentration, some studies have shown that low levels was a non-significant predictor of ICU mortality [24,32]. A study by Morris et al., reported that higher levels of serum albumin were significantly associated with an increased odds of survival [25]. Our study did not find any difference the mean serum albumin concentration between patients that survived and those that died.

In keeping with findings of other studies [26,33,34], there were statistically significant differences in both the median APACHE II score and the median SOFA score between those that died and those that survived. Although the RAMR of 0.51 in this study may be a pointer of quality of ICU care, it may also indicate that the APACHE II score has a tendency to overestimated mortality in HIV infected ICU patients by approximately two-fold. This ratio has not been previously reported in other similar studies.

LIMITATIONS

There are some limitations to this study. It is a single centre, retrospective study with a relatively small sample size that was conducted over a one-year period. Selection bias could also not be avoided as admission to the ICU was at the discretion of the ICU specialist on call. In addition, some data such as the CD4 cell count may have been influenced by the underlying disease process of the patient and may not have reflected the patients pre-morbid state. Adherence to ART could in addition not be determined. Furthermore, our study did determine outcomes and survival after hospital discharge. Despite these limitations, this study is of significant value, being one of the few studies of this nature to be conducted in a developing country.

CONCLUSION

Age, length of stay in ICU, primary diagnostic category, sepsis acquired during ICU stay, requirement for inotropic/vasopressor support, requirement for mechanical ventilation, requirement for haemodialysis, CD4 cell count, APACHE II score and SOFA score were significantly associated with ICU mortality in HIV positive patients. The APACHE II score may have a tendency to overestimate mortality in HIV infected ICU patients. Hence, the treatment and management of HIV infected patients in the ICU should be individualized, as outcome is more likely related to the severity of the underlying disease process rather than the HIV status.

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RESEARCH PROTOCOL

AN AUDIT OF HIV PATIENTS ADMITTED TO A MULTIDISCIPLINARY TERTIARY LEVEL INTENSIVE CARE UNIT

Research protocol in partial fulfilment of the degree for Master of Medicine (Emergency Medicine)

Dr Rammona Wayne Maphula

Student No. 0504807J

Supervisors: Professor Abdullah E Laher

Professor Guy A Richards

INTRODUCTION

HIV is a global healthcare problem, with over 38.8 million people living with HIV at the end of 2015 [1]. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS) 2016 estimates, Eastern and Southern Africa were the world's most affected regions, with an estimate of 19 million people living with HIV in 2015 and 960 000 new infections amongst all ages [2]. South Africa has the largest epidemic with an estimated 6.4 million people infected with HIV, the highest prevalence being amongst young women [3,4].

Prior to antiretroviral therapy (ART) availability, HIV accounted for over 50% of admissions in public sector hospitals, with TB and bacterial infections being the most common cause of

admission [3]. This had profound negative effects on households, communities and governments including a decline in household wealth, a large increase in the number of orphans, loss of skilled workers and the interruption of inter-generational transmission of knowledge and norms [5].

ART has been available in South Africa since 2004. Currently there are more than 2.5 million South Africans receiving ART's, which has improved the life expectancy of people living with HIV to around 80% of normal life [6,7]. Since 2016, ART has been made available to all South Africans in the public sector irrespective of the CD4 cell count [8].

Health deterioration in HIV positive individuals may be due to a number of reasons that include denial, poor compliance/adherence to ART's, ART drug resistance and drug-related toxicities [9]. Reasons for poor compliance include poor education, forgetting to take the medication, unavailability of stock at the dispensing site, occupation, large number of tablets which are considered to be too much to consume, work related travel, side effect intolerance, lack of food, financial crisis, depression and poor social support [10,11].

With the introduction of ART, there has been an improvement in intensive care unit (ICU) and hospital survival. There are various reasons that patients with HIV may require admission to the ICU, these include severe HIV associated illnesses (e.g. opportunistic infections, malignancy), complications of ART medications and HIV unrelated pathology [12]. Sepsis is amongst the commonest reasons for ICU admission among HIV positive patients. According to some studies, the rate of HIV related ICU admission has remained constant, but others suggest that that it has improved since onset of the epidemic [13]. Studies have shown that approximately 5-10% of all

hospitalized HIV infected patients require ICU admission, 40% of whom are only diagnosed with HIV on ICU admission and 50% of those with a known diagnosis of HIV had not been initiated on ART at the time of ICU admission [14,15].

Risk factors for poor short term survival after ICU discharge were found to be similar in HIV positive and negative subjects. These include poor baseline health, higher severity of acute illness and delayed delivery of critical care. Factors associated with worse ICU outcomes include a high Acute Physiology and Chronic Health Assessment (APACHE) II score, low albumin levels, requirement of vasopressors or inotropes, need for mechanical ventilation, PCP diagnosis and other AIDS-related illnesses. Surprisingly, the CD 4 cell count and HIV viral load were not shown to predict ICU survival [15,16].

Critical care medicine has always been a significant part of emergency medicine. Its practice in the emergency department (ED) has never been as prevalent as it is today [17]. With persistent problems of hospital overcrowding and ED boarding, emergency physicians are now managing critically ill patients in the ED for prolonged periods after initial resuscitative efforts [18]. A study reported that only 53.3% of all ED requests for ICU beds were accepted, thus leaving a substantial proportion of critically ill patients boarding in the ED for prolonged periods [19]. Therefore, due to the high prevalence of HIV in South Africa, it is imperative for ED clinicians to have good insight with regards to the presentation and outcome of HIV infected patients in the ICU.

STUDY AIM

The aim of this study is to conduct an audit of HIV infected patients admitted in the ICU

STUDY OBJECTIVES

1. To determine the reasons (diagnosis) for ICU admission of HIV infected patients to the ICU.
2. To describe the specific HIV related history (date of first diagnosis, ART treatment regimen, ART compliance, latest CD4 cell count and latest HIV viral load).
3. To describe outcomes and final disposition of patient, i.e. survival to discharge from ICU, survival to hospital discharge and total length of ICU stay.
4. To determine if there is an association between requirements for vasopressor/inotropes, mechanical ventilation, haemodialysis as well as other variables with survival to ICU discharge.

METHODS

Study design

The study will be a single-centre, retrospective audit of medical records

Study site

This study will be conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) adult general Intensive Care Unit, areas 576 and 577.

Study population

Patients with confirmed HIV infection that had been admitted to the CMJAH ICU, over the study period.

Inclusion criteria

All HIV positive patients admitted to the CMJAH ICU from 01 January 2017 until 31 December 2017.

Sample size estimation

CMAJH ICU admits approximately 90 patients per month. Since, the national estimate of patient with HIV between the ages of 15 to 49 years is 18%, it is estimated that the ICU admits about 16 patients with HIV per month. Therefore, it is estimated that the study sample size will comprise of approximately 200 subjects over a period of 1 year.

Data collection

- Data collection will commence after the necessary approvals and permissions have been granted.
- The ICU register will be used to identify files of patients that have been admitted to the ICU over the study period.
- All patient records over the study period will be screened to identify patients with HIV.
- Data will be abstracted by the researcher from patient files that meet the inclusion criteria.
- The abstracted data will be recorded on the data collection sheet (below).
- The collected data will be analysed by the researcher.
- It will be ensured that the data collection process will not interfere with the researcher's clinical duties and responsibilities.

DATA ANALYSIS

Analysis will be carried out using Stata version 15 (StataCorp Limited, Texas, United States of America). Where indicated, mean and standard deviation (SD) or median and interquartile range (IQR) of various variables will be reported. Where appropriate, the Student's t-test, Mann-Whitney rank sum test, Pearson's Chi squared test or the Fisher's exact test will be used to compare sociodemographic details, primary diagnosis, ICU sepsis, requirement for

inotrope/vasopressor support, mechanical ventilation, haemodialysis, surgical procedures performed during ICU stay, HIV diagnosed after ICU admission, ART initiation prior to ICU admission, HIV viral load, median CD4 cell count, median serum albumin level, median APACHE II score, median SOFA score and length of ICU stay between patients that survived and those that died. Using univariate logistic regression, the odds ratios (OR) for ICU mortality will be determined for each variable. Factors showing a possible association (defined as a p-value of ≤0.1 on univariate analysis) will be included as covariates in a multivariate logistic regression model. A two-sided p-value of <0.05 will be considered significant throughout.

ETHICS

Permission to conduct the study will be obtained from the CEO of the hospital and the Head of Department of the ICU. Permission will also be obtained from the Human Research Ethics Committee of the University of the Witwatersrand.

TIMING

2018	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec
Literature review	■	■	■									
Preparing protocol		■	■									
Protocol assessment			■									
Ethics application			■	■								
Collecting data					■	■	■	■				
Data analysis								■	■	■		
Write up										■	■	■

FUNDING

No major cost is expected. All minor costs will be borne by the researcher as follow:

Stationary – R 500.00

Travelling – R 500.00

Total – R 1 000.00

PROBLEMS

It is likely that some information will not be available in the patient's hospital records and some hospital records may be missing.

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DATA COLLECTION SHEET

Subject Number: _____

Date of ICU admission:		**Date of ICU discharge / death (specify):**	

Demographics

Age:		**Gender:**	M	F	**Nationality:**	RSA	Other:

Employment:	Y	N	Where:

HLOE:	None	Std5/Grd7	Std8/Grd10	Std10/Grd12	University

APACHE 2 score: **SOFA score:**

Final diagnosis / assessment (including complications developed during ICU stay):

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Co-morbidities on ICU admission: Diabetes mellitus / hypertension / past medical history or other (specify):

_____
_____
_____

Sepsis acquired during ICU stay: Y / N, if yes specify site, organisms cultured, antibiotics used (including duration):

_____
_____
_____
_____
_____

Inotrope/ vasopressor required during ICU admission: Y / N

If yes, specify agent/s used, highest dose required and total duration per agent:

_____
_____
_____
_____
_____
_____

Other medications:

<u>Mechanical ventilation required during ICU stay</u>: Y / N
If yes, specify no. of days and mode of ventilation:
_____

<u>Haemodialysis required during ICU stay</u>: Y / N
If yes, specify no. of days and mode of dialysis:
_____

<u>Surgical procedures during this admission</u>: Y / N, if yes, specify type of procedure, number of procedures, relook procedures:
_____
_____
_____
_____
_____
_____

<u>HIV related history</u>

First diagnosed (date):											
Newly diagnosed on this admission:			Y			N					
ART treatment:	Y	N	If yes, regimen:								
ART compliance:	Y	N	If no, reasons:								
Latest CD4 cell count / date:					**Latest viral load / date:**						
<u>Vital signs on ED/hospital admission</u>											
HR:		**BP:**		**RR:**		**O_2 Sats:**		**Temp:**		**HGT:**	

<u>Laboratory findings on ED/hospital admission</u>

FBC:	
U+E:	
LFT:	
CMP:	
Albumin	
INR/PTT:	
CRP / PCT:	
LP:	
Blood Gas:	

Sputum:	
Other significant findings (specify):	
Patient Disposition / outcome	
Survival to discharge from ICU: Y / N	**Survival to hospital discharge: Y/N**
Total duration of ICU stay (days) **_____**	**Cause of death (if applicable):** **_____** **_____** **___**

APPENDIX 1: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr RW Maphula

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180346

NAME: (Principal Investigator)	Dr RW Maphula
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Emergency Medicine Intensive Care Unit Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	An audit of HIV patients admitted to a mult-disciplinary tertiary level Intensive Care Unit
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A Laher and Professor G Richards
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/06/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

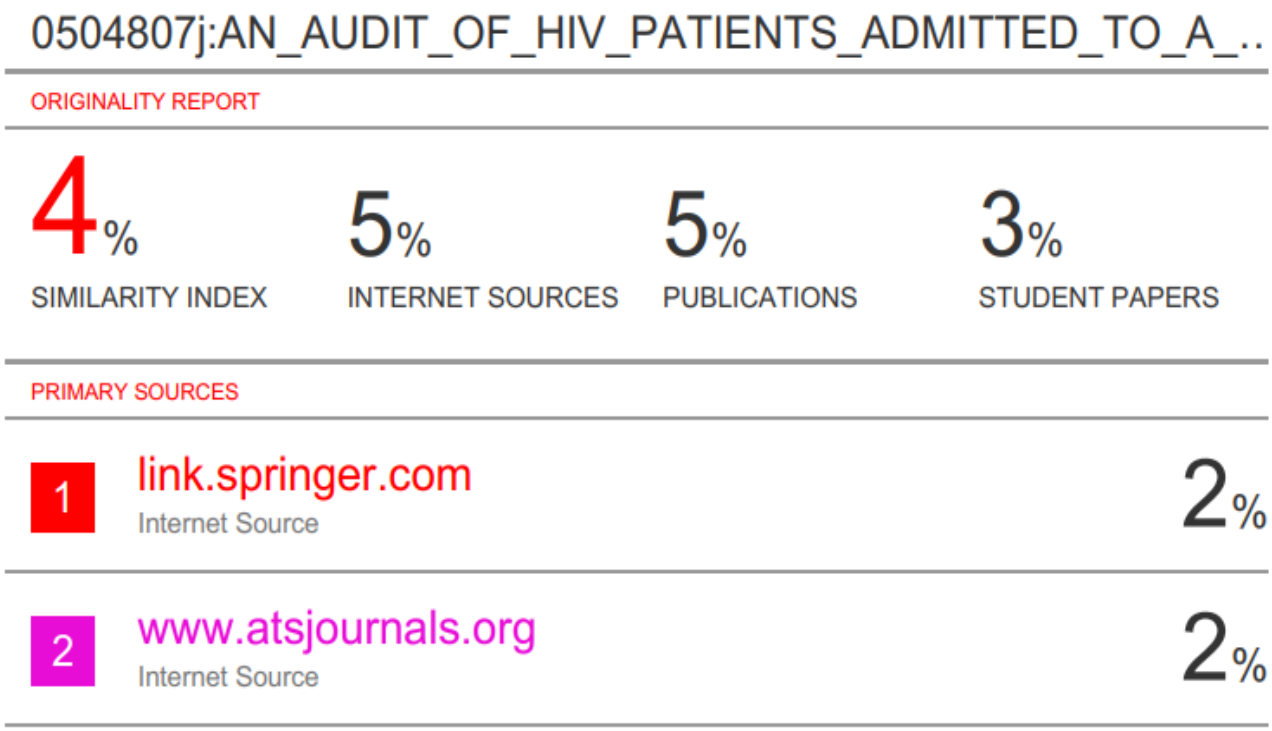
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 03/06/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2: TURN-IT-IN PLAIGIRISM REPORT



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