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HIV-positive patients in the intensive care unit: A retrospective audit

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Background. The indications for and outcomes of intensive care unit (ICU) admission of HIV-positive patients in resource-poor settings such as sub-Saharan Africa are unknown.
Objective. To identify indications for ICU admission and determine factors associated with high ICU and hospital mortality in HIV-positive patients.
Methods. We reviewed case records of HIV-positive patients admitted to the medical and surgical ICUs at Groote Schuur Hospital, Cape Town, South Africa, from 1 January 2012 to 31 December 2012.
Results. Seventy-seven HIV-positive patients were admitted to an ICU, of whom two were aged <18 years and were excluded from the final analysis. HIV infection was newly diagnosed in 37.3% of the patients admitted during the study period. HIV-positive patients had a median CD4 count of 232.5 (interquartile range 59 - 459) cells/μL. Respiratory illness, mainly community-acquired pneumonia, accounted for 30.7% of ICU admissions. ICU and hospital mortality rates were 25.3% and 34.7%, respectively. Predictors of ICU mortality included an Acute Physiology and Chronic Health Evaluation II (APACHE II) score >13 (odds ratio (OR) 1.4, 95% confidence interval (CI) 1.1 - 1.7; p=0.015), receipt of renal replacement therapy (RRT) (OR 2.2, 95% CI 1.2 - 4.1; p=0.018) and receipt of inotropes (OR 2.3, 95% CI 1.6 - 3.4; p<0.001). Predictors of hospital mortality were severe sepsis on admission (OR 2.8, 95% CI 0.9 - 9.1; p=0.07), receipt of RRT (OR 1.9, 95% CI 1.0 - 3.6; p=0.056) and receipt of inotropic support (OR 2.0, 95% CI 1.4 - 3.2; p<0.001). Use of highly active antiretroviral therapy (HAART), CD4 count, detectable HIV viral load and diagnosis at ICU admission did not predict ICU or hospital mortality.
Conclusions. Respiratory illnesses remain the main indication for ICU in HIV-positive patients. HIV infection is often diagnosed late, with patients presenting with life-threatening illnesses. Severity of illness as indicated by a high APACHE II score, multiple organ dysfunction requiring inotropic support and RRT, rather than receipt of HAART, CD4 count and diagnosis at ICU admission, are predictors of ICU and hospital mortality.

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HIV/AIDS is a major public health burden, with an estimated 35.3 million people infected globally.[1] Sub-Saharan Africa (SSA) bears the brunt of the pandemic, with 25 million HIV-positive people living in the region.[1] The advent of highly active antiretroviral therapy (HAART) has changed the natural history of HIV/AIDS, with a reported decline in mortality from 24.5 per 100 person-years in 1995 to 8.9 per 100 in 1997,[2] and reportedly 2.1 per 100 in 2010.[3] Today HIV-positive patients in high-income countries are reported to have a life expectancy approaching that of the general population.[4] Despite evidence of the role of HAART in decreasing morbidity and mortality in HIV-positive patients, in resource-poor settings many people living with HIV do not have access to HAART or receive treatment late. Globally, only 9.7 million people were estimated to be receiving HAART in 2012.[5] Many HIV-positive people present with serious illnesses that may require intensive care unit (ICU) admission,[6] and a large proportion of these are unaware of their HIV status.[7] Data from high-income countries suggest that 7 - 12% of HIV-positive patients admitted to hospital are treated in the ICU.[8,9]

Historically, respiratory failure accounted for the majority of ICU admissions in the HIV-positive patient population, with an associated mortality of ~70%.[9,10] However, contemporary evidence from high-income countries suggests that ICU outcomes are similar to those of HIV-negative patients and that the indications for ICU are mostly not related to opportunistic infections (OIs).[10,11]

ICU utilisation and outcomes for HIV-positive patients in poorly resourced settings, where access to both intensive care and HAART is limited, have not been widely studied. With an increasing prevalence of HIV and an unchanging (and at times decreasing) number of available ICU beds, it is imperative to know the profile and outcome of HIV-positive patients requiring ICU admission in a resource-poor setting such as South Africa (SA).

Objective

To identify indications for ICU admission and determine factors associated with high ICU and hospital mortality in HIV-positive patients admitted to ICUs in a resource-limited setting. This will help in determining the appropriateness of offering ICU care to HIV-positive patients and in the appropriate development of policies and planning for allocation of limited resources.

Methods

Study design and patient population

The study was a retrospective folder review conducted from 1 January 2012 to 31 December 2012 in the medical and surgical ICUs at Groote Schuur Hospital (GSH), Cape Town, SA. GSH is a tertiary hospital affiliated to the University of Cape Town (UCT), and is an 867-bed institution with 16 general medicine and general surgery adult ICU beds (excluding the coronary care unit, the neurosurgical ICU and

the cardiothoracic ICUs). The GSH ICUs admit all patients deemed to require ICU care, irrespective of the need for ventilation. At the time of the study, GSH did not have a high-care unit. The GSH ICUs have no ICU admission criteria, admission being at the discretion of the treating or referring physician and the ICU physician on call at the time of ICU referral.

Patients were enrolled in the study if they were aged >18 years at the time of ICU admission, known to be HIV-positive, or newly diagnosed with HIV in the index admission.

Ward admission books and CLINICOM (a health information system including demographic and clinical patient data and providing a single electronic patient record that is accessible throughout the Western Cape Province of SA) records were interrogated for information on all the patients admitted to an ICU during the study period. Patient folders and laboratory records were examined for the results of HIV tests done during and prior to the index admission and for patient diagnoses during ICU admission.

Ethical approval

The study was carried out with the approval of the GSH and UCT Human Subjects Research Ethics Committee (ref. no. 044/2013). The need to obtain informed consent was waived, as this was a retrospective study and no identifying details would be included.

Case definition

Patients were coded as HIV-negative if they had had a negative HIV test 3 months prior to the index admission, and as untested if there was no documented HIV test result in the folder or no recorded HIV test in the National Health Laboratory Service electronic records. HIV infection was diagnosed by two positive antibody tests or one positive antibody test and a confirmatory Western blot test. No HIV testing was offered or done for the purpose of this study.

Data collection

A standardised form was used to collect demographic information, including age, sex and ethnic group. Details of length of ICU and hospital stay, use of mechanical ventilation and inotropic support were also recorded. The most recent CD4 count and HIV viral load, when available, were recorded. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated using laboratory values obtained within 24 hours of ICU admission. Use of HAART before hospital admission was recorded. The presence of acute kidney injury (AKI) (as defined by Kidney Disease Improving Global Outcomes) on admission to the ICU and the use of renal replacement therapy (RRT) were documented.[12] Diagnoses at ICU admission were categorised by organ system and severity of sepsis.[13]

Statistical analysis

Data analysis was performed using SPSS version 20 (IBM, USA). Normality of data was tested using the Kolmogorov-Smirnov test. Normally distributed data are presented as means (standard deviation (SD)) or, where highly skewed, as medians (interquartile range (IQR)); discrete data are presented as numbers (percentages). The χ^2 test or Fisher's exact test was utilised to compare discrete data, as appropriate. In an attempt to identify factors associated with ICU and hospital mortality in HIV-positive individuals, HIV-positive patients who died in the ICU were compared with HIV-positive patients who were discharged alive from the ICU, and HIV-positive patients who died in hospital were compared with HIV-positive patients who were discharged alive. Analysis of variance with post-hoc Bonferroni correction was used to explore whether there were differences between the groups. Bivariate correlations were assessed using the Pearson r and Spearman r_S coefficients, as appropriate. All statistical tests were two-tailed, with $p<0.05$ considered significant.

Results

From 1 January 2012 to 31 December 2012, 806 patients were admitted to the ICUs. Of these, 77 were HIV-positive, giving an incidence of 9.6 per 100 person-years. Two patients were aged <18 years and were excluded from the final analysis (Fig. 1). Two hundred and thirty-seven patients (29.4%) were HIV-uninfected or had tested HIV-negative during the 3 months prior to ICU admission. HIV status was unknown for 492 patients admitted to the ICUs (61.0%).

Patient demographic and clinical characteristics at ICU admission

A total of 75 patients were included in the analysis, with a mean (SD) age of 36.5 (9.6) years (Table 1). In keeping with the epidemiology of HIV infection in SSA, the majority of patients were female (64.0%). The CD4 count was available for 74 of the 75 patients. The median CD4 count was 232.5 (IQR 59 - 459) cells/μL. The HIV viral load was available for 27 patients, all of whom were receiving HAART at the time of ICU admission. Thirteen of the 27 patients had a detectable HIV viral load. The mean HIV viral load was 2 218 556.5 RNA copies/mL and the median HIV viral load was 20 146.5 (IQR 372.75 - 25 898.75) RNA copies/mL. More than a third of the patients (37.3%) were newly diagnosed with HIV during the index hospital admission (Table 1).

Thirty-nine patients (52.0%) were not receiving HAART. The mean (SD) duration of HAART was 6.3 (17.5) months. No patients were started on antiretroviral therapy during their ICU stay.

ICU admission occurred after a median of 2 (IQR 1 - 6) days in the referring unit; 33 patients (44.0%) were admitted to the ICU within 24 hours of arrival in hospital, 17 (22.7%) between 24 and 72 hours after arrival, and 25 (33.3%) >72 hours after arrival (Fig. 2). Thirty-one patients (41.3%) were referred to the ICU from the general medical wards, 20.0% from casualty (medical emergency), 16.0% from the general surgical wards, 12.0% from the trauma ward and 10.7% from maternity (Table 1). Approximately one-third (30.7%) of the patients were admitted to the ICU for respiratory illnesses. Fifteen of the patients with respiratory illness had community-acquired pneumonia, four had pulmonary tuberculosis (initially referred to the ICU as community-acquired pneumonia) and the other four had *Pneumocystis jirovecii* pneumonia. The diagnosis of *P. jirovecii* pneumonia was made after ICU admission. Two of the

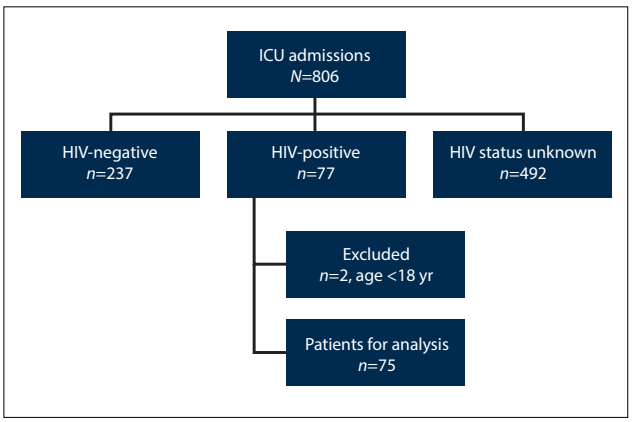

Fig. 1. Flow diagram showing patient enrolment. (ICU = intensive care unit.)

Table 1. Patient characteristics (*N*=75)

Age (years), mean (SD)	36.5 (9.6)
Female (%)	64.0
Race (%)	
Black	84.0
Mixed race	16.0
Newly diagnosed HIV (%)	37.3
On HAART (%)	48.0
Duration of HAART (months), range	0 - 72
CD4 count (cells/μL), median (IQR)	232.5 (59 - 459)
Detectable HIV viral load (%)	18.7
Prior HIV-related illnesses (%)	
Tuberculosis	25.3
Syphilis	1.3
HIV-associated nephropathy	1.3
Source of referral (%)	
Emergency unit*	32.0
Medical ward	41.3
Surgical ward	16.0
Maternity	10.7
Number of days in the referring unit, median (IQR)	2 (1 - 45)
Diagnoses at ICU admission (%)	
Respiratory illness	30.7
Severe sepsis	13.3
Trauma	12.0
Drug toxicity and poisoning	8.0
Neurological illness	9.3
Elective surgery	8.0
Other†	18.7
APACHE II score, mean (SD)	21.6 (8.4)
AKI on admission (%)	26.7
Mechanical ventilation (%)	90.7
RRT (%)	32.0
Inotropic support (%)	50.7
ICU complications (%)	
AKI	16.0
Sepsis	25.3
AKI and sepsis	17.3
Number of days in ICU, median (IQR)	4 (2 - 8)
Number of days in hospital, median (IQR)	16 (9 - 34)

SD = standard deviation; HAART = highly active antiretroviral therapy; IQR = interquartile range; ICU = intensive care unit; APACHE II = Acute Physiology and Chronic Health Evaluation II; AKI = acute kidney injury; RRT = renal replacement therapy.
*Includes medical emergency (casualty) and trauma unit.
†Includes patients admitted with renal illness, malaria, gastrointestinal illness, emergency surgery and cardiac illness.

patients diagnosed with *P. jirovecii* pneumonia had a new diagnosis of HIV infection. The other two patients with *P. jirovecii* pneumonia were known to be HIV-positive and were receiving HAART; their CD4 counts were <150 cells/μL, and both had a detectable HIV viral load. Ten patients had pulmonary tuberculosis and were receiving antituberculosis therapy before ICU admission. Nineteen patients had previous tuberculosis, which had been fully treated.

Patient clinical characteristics during the ICU stay

The majority of the patients (90.7%) required mechanical ventilation, and 50.7% required inotropic support. Fifty-five patients (73.3%) had AKI on admission to the ICU. RRT was offered to 24 patients (32.0%). Patients presented with a mean (SD) APACHE II score of 21.6 (8.4). The median numbers of days in the ICU and in hospital were 4 (IQR 2 - 8) and 16 (IQR 9 - 34), respectively.

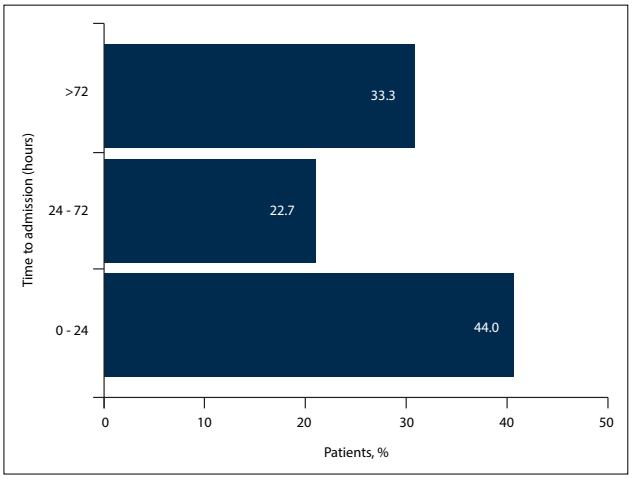

Fig. 2. Time in the referring unit prior to intensive care unit admission.

ICU and hospital mortality

Nineteen patients (25.3%) died in the ICU, an additional 7 patients died in hospital after ICU discharge (9.3%), and 49 (65.3%) were discharged from hospital alive. Use of RRT was significantly associated with mortality in the ICU (odds ratio (OR) 2.2, 95% confidence interval (CI) 1.2 - 4.1; p=0.018), but not with hospital mortality (OR 1.9, 95% CI 1.0 - 3.6; p=0.056) (Table 2). The use of inotropes in the ICU was associated with both ICU (OR 2.3, 95% CI 1.6 - 3.4; p<0.001) and hospital mortality (OR 2.0, 95% CI 1.4 - 3.2; p<0.001). An APACHE II score of >13 at ICU admission was also significantly associated with increased ICU mortality (OR 1.4, 95% CI 1.1 - 1.7; p=0.015), but not hospital mortality (OR 1.3, 95% CI 1.0 - 1.6; p=0.066). The number of days in the referring unit prior to ICU admission did not predict death in the ICU (p=0.075) or in hospital (p=0.191). Factors including CD4 count, use of HAART, mechanical ventilation, serum albumin and whether the patient was known to have or was newly diagnosed with HIV infection were not significantly associated with increased ICU or hospital mortality.

Discussion

The key findings of our study were: (*i*) that respiratory illnesses remain the major indication for ICU admission in HIV-positive patients; (*ii*) that there were ICU and hospital mortality rates of 25.3% and 34.7%, respectively, in a contemporary SA setting; and (*iii*) that factors associated with poor short-term outcomes in HIV-positive patients admitted to the ICU were the use of RRT, vasopressor support and an APACHE II score >13. To our knowledge, this is the first study that has determined the outcomes of HIV-positive adults admitted to an SA ICU. These results have implications for resource allocation and management of HIV-positive patients requiring ICU care in resource-constrained settings. They suggest that sicker patients, as suggested by higher APACHE II scores and the need for organ support such as RRT and inotropes in the setting of HIV infection, have worse outcomes. In resource-limited settings, ICU care may have to be withheld from HIV-positive patients who meet the above criteria. Furthermore, these results support the general criteria for ICU admission used in the SA public sector, which take into account the severity of the clinical presentation and the likelihood of reversibility of organ dysfunction.[14]

Table 2. Patient outcomes according to specific variables

	Death in ICU, *n*	OR (95% CI)	*p*-value	Death in hospital, *n*	OR (95% CI)	*p*-value
Female (*N*=48)	15	1.2 (0.8 - 1.7)	0.403	16	0.9 (0.7 - 1.4)	0.746
Respiratory illnesses (*N*=23)	6	1.1 (0.5 - 2.3)	0.755	7	1.8 (0.4 - 1.7)	0.609
Severe sepsis (*N*=10)	3	1.1 (0.3 - 3.9)	0.880	6	2.8 (0.9 - 9.1)	0.071
AKI on admission (*N*=20)	7	1.7 (0.8 - 3.6)	0.163	8	1.3 (0.6 - 2.7)	0.558
Mechanical ventilation (*N*=68)	20	1.0 (0.9 - 1.2)	0.396	25	1.1 (1.0 - 1.2)	0.234
Renal replacement therapy (*N*=24)	11	2.2 (1.2 - 4.1)	0.018	12	1.9 (1.0 - 3.6)	0.056
Inotropic support (*N*=38)	18	2.3 (1.6 - 3.4)	<0.001	20	2.0 (1.4 - 3.2)	0.001
APACHE II >13 (*N*=57)	20	1.4 (1.1 - 1.7)	0.015	23	1.3 (1.0 - 1.6)	0.066
Newly diagnosed HIV (*N*=28)	10	1.4 (0.8 - 2.6)	0.251	11	1.2 (0.7 - 2.2)	0.516
Not on HAART (*N*=39)	13	1.3 (0.8 - 2.0)	0.284	16	1.3 (0.9 - 2.0)	0.228
Detectable HIV viral load (*N*=13)	4	1.3 (0.6 - 2.8)	0.580	5	1.3 (0.6 - 2.7)	0.586
CD_4 count <200 cells/μL (*N*=35)	12	1.4 (0.9 - 2.3)	0.183	15	1.5 (0.9 - 2.3)	0.118
Time in the referring unit (hours)			0.075			0.191
<24 (*N*=33)	9			12		
24 - 72 (*N*=17)	1			3		
>72 (*N*=25)	9			14		

ICU = intensive care unit; OR = odds ratio; CI = confidence interval; AKI = acute kidney injury; APACHE II = Acute Physiology and Chronic Health Evaluation II; HAART = highly active antiretroviral therapy.

Intensive care for HIV-positive patients was initially remarkable for high ICU and hospital mortality,[15,16] and in keeping with previous reports we found an ICU mortality rate of 25.3%.[10,17,18] Respiratory illnesses remain the leading diagnoses at ICU admission in HIV-positive patients.[9,10] It has been reported that mechanical ventilation for respiratory illnesses is associated with poor ICU outcomes.[9,19-22] In this SA cohort, respiratory illnesses represented the most common indication for ICU admission, but were not associated with increased ICU and hospital mortality. We also did not find an association of mechanical ventilation with ICU and hospital mortality. In a study by Casalino *et al*.,[22] 45% of the patients with respiratory illnesses had *P. jirovecii* pneumonia. In the HAART era, the incidence of *P. jirovecii* pneumonia in HIV-positive patients admitted to ICUs has decreased to 3 - 9%.[10,11] Up to 50% of HIV-positive patients are unaware of their HIV status prior to ICU admission.[7,23-25] Compared with patients who are known to be HIV-positive prior to ICU admission, this patient group is characterised by pronounced immunosuppression and typically admitted with AIDS-related diagnoses such as *P. jirovecii* pneumonia.[10,23,25-27] The frequency of newly diagnosed HIV-positive patients at ICU admission has remained relatively the same in the HAART era as in the pre-HAART era, but the frequency of OIs in the ICU has decreased.[7,9] Only 5.3% of our patients had *P. jirovecii* pneumonia. The diagnoses of *P. jirovecii* pneumonia was made during their ICU stay. *P. jirovecii* pneumonia, the need for mechanical ventilation in *P. jirovecii* pneumonia, development of a pneumothorax in *P. jirovecii* pneumonia and ICU admission for an AIDS-related diagnosis are widely thought to be related to high ICU and hospital mortality.[8,17,19,24,28] We do not have information on the number of HIV-positive patients who might have qualified for ICU care but were not referred to an ICU or were turned down for admission. This would help determine the reasons behind the denial of ICU care in this patient population and whether physician attitudes towards ICU care for HIV-positive patients have changed.

The severity of the acute event as marked by high APACHE II scores,[9,28-30] the use of inotropes[27,31,32] and RRT[33] is reported to be associated with poor short-term outcomes. In this study, we found that a high APACHE II score, use of inotropes and RRT were significantly associated with both ICU and hospital mortality in HIV-positive patients. Their presence in areas where resources are constrained could be used to determine whether ICU admission is warranted or intensive support should be initiated.

Between 24% and 50% of HIV-positive patients receive HAART prior to ICU admission.[8,10,23,26] Receipt of HAART prior to ICU admission has been associated with contradictory results in terms of association with short-term outcomes. Some authors have reported increased survival rates in patients on HAART prior to ICU admission, while others have reported that receipt of HAART did not predict short-term outcomes.[7,8,11,27] In our study, 48.0% of the patients were on HAART prior to ICU admission, but HAART prior to ICU admission did not predict ICU and hospital survival. Reports have shown that HIV viral load and CD4 count did not predict ICU and hospital survival.[11,27,28] Similarly, in our study we did not find any statistically significant association between detectable HIV viral load, low CD4 count and short-term outcomes in terms of either ICU or hospital mortality.

Up to 50% of HIV-positive persons have severe sepsis at ICU admission, or suffer from severe sepsis during their ICU stay.[32] Many infections responsible for sepsis in this patient population are nosocomial, followed by AIDS-related infections.[29] Ward stay prior to ICU admission is a risk factor for sepsis in HIV-positive patients.[32] Severe sepsis has been reported to be associated with poor ICU outcomes in HIV-positive patients.[32] In our study, 13.3% of the patients had a diagnosis of severe sepsis at ICU admission, and 42.6% acquired severe sepsis during their ICU stay. We did not find an association between severe sepsis and death in this cohort.

The fact that 52.0% of the patients in our cohort were not receiving HAART, and 18.7% had a detectable HIV viral load while receiving HAART, suggests that improving ICU care plays a major role in the better outcomes of HIV-positive patients in the ICU. In our hospital, we have adopted lung-protective ventilation, surviving sepsis guidelines and appropriate glucose control in our ICUs.[34,35] There were very few case of *P. jirovecii* pneumonia, which may account for the apparent lack of association between respiratory illnesses, mechanical ventilation and death.

Study limitations

Our study has several important limitations: (*i*) it is a single-centre study; (*ii*) it suffers from the limitations and biases of its

retrospective nature; (*iii*) we were not able to find and document the microbiological causes of all the cases of community-acquired pneumonia, which could offer an opportunity for prophylaxis; and (*iv*) most importantly, 61.0% of our ICU population did not have an HIV test. Considering that our community has a high prevalence of HIV infection, this represents a missed opportunity for testing and potential treatment.

Conclusions

This study shows that critical care outcomes for HIV-positive patients at GSH are comparable to those in the developed world. As these are findings from a tertiary care unit, they are not representative of the rest of the country. The study highlights the fact that ICU outcomes for this patient population depend on the severity of the acute illness, irrespective of receipt of HAART and immune status. More research is needed that is representative of poorer provinces of SA and the rest of the African continent.

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