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HIV Positive Patients In Intensive Care – A Retrospective Chart review

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfillment of the requirements for the degree of

MASTER OF MEDICINE (MMed – mini-dissertation)

Faculty of Health Sciences

Declaration of originality

This research report is my original work. Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. None of this work has been published in any format prior to registration for the abovementioned degree

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Thesis Abstract

Background:

The indications for and outcomes of intensive care unit (ICU) admission of HIV-infected patients in resource-poor settings like Sub-Saharan Africa are unknown.

Methods:

We reviewed case records of HIV-infected patients admitted to the medical and surgical ICUs at Groote Schuur Hospital, South Africa from 1 January 2012 to 31 December 2012. HIV infection was defined as two positive antibody tests.

Results:

Seventy seven HIV-infected patients were admitted to ICU, 2 were younger than 18 years and were excluded from the final analysis. HIV infection was newly diagnosed in 37.3% of the patients admitted during this period. HIV-positive patients had a mean (± standard deviation) CD_4 count of 293.9×10^6/L $\pm$ 247.2×10^6/L. Respiratory illness accounted for 30.7% of ICU admissions, community-acquired pneumonia was responsible for the majority of the respiratory cases. ICU and hospital mortality was 25.3% and 34.7% respectively. Predictors of ICU mortality included an APACHE II score >13 (Odds Ratio {OR}, 1.4; 95% confidence interval {CI} 1.1-1.7; p value 0.015), receipt of renal replacement therapy (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 renal replacement therapy (OR, 1.9; 95% CI 1.0-3.6; p 0.056), receipt of inotropic support (OR, 2.0; 95% CI 1.4-3.2; p 0.001). Use of highly active antiretroviral therapy, CD4 count, detectable HIV viral load and the diagnoses at ICU admission did not predict ICU or hospital mortality.

Conclusion

Respiratory illnesses remain the main indication for ICU in HIV infected patients. HIV is diagnosed late with patients presenting in dire straits. Receipt of HAART, CD4 count and the diagnoses at ICU admission are not predictors of ICU or hospital mortality, but rather the severity of illness as indicated by a high APACHE II score, multiple organ dysfunction requiring inotropic support and renal replacement.

1.1 **Chapter** 1

HIV sero-positive adults In Intensive Care Unit – Literature review

1.1.1 Introduction

Acquired Immunodeficiency syndrome (AIDS) is the most severe manifestation of a clinical spectrum of illness caused by infection with Human Immunodeficiency Virus (HIV). AIDS is defined by the development of serious opportunistic infections, neoplasms, or other life threatening manifestations resulting from profound progressive HIV-induced immunosuppression. AIDS was first recognized in mid 1981, when unusual clusters of *Pneumocystis jirovecii* pneumonia and Kaposi's sarcoma were reported in young, previously healthy homosexual man in New York City, Los Angeles and San Francisco (1). Two years after the first reports of AIDS, a retrovirus, Human Immunodeficiency Virus was isolated from the persons with AIDS and associated conditions (2). In 1985, serologic tests to detect evidence of infection with HIV were developed to identify those infected with the virus and to protect blood products (1).

Today, HIV remains a major public health burden, with an estimated 35.3 million people infected globally. Sub-Saharan Africa bears the brunt with 25 million HIV-infected people living in the region (3). The advent of antiretroviral therapy (ART) 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 person-years in 1997 (4). Despite the good evidence of the role of antiretroviral therapy in decreasing morbidity and mortality in HIV/AIDS patients, most people living with HIV do not have access to ART. Globally, only 9.7 million people were estimated to be receiving ART in 2012 (5). The vast majority of HIV-infected people present with advanced disease characterized by severe opportunistic infections (6). Large numbers are unaware of their HIV status and present for the first time with severe illnesses requiring intensive care (7). Between 7 and 12% of HIV-positive patients admitted to hospital are treated in an Intensive Care Unit (ICU) (8, 9).

This literature review describes published evidence of the admission of patients with HIV/AIDS to an ICU. The attention is focused on the indications for admission to intensive care, the outcomes of the patients that were admitted to intensive care, and the changes in these variables over time.

1.1.2   <u>Methods</u>

A literature search from 1981 to 2013 was performed using MEDLINE. Papers containing the terms Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome and Intensive Care Unit or critical care were identified and assessed to determine whether they met the inclusion criteria for the review. Inclusion criteria were:

- HIV-positive patients admitted to Intensive Care Unit

- Adults

- Full text available

- English language

The reference list of papers that satisfied the inclusion criteria were scrutinized to identify papers not identified in the original search process.

1.1.3   <u>Results</u>

<u>1980-1995 (Table 1)</u>

Pneumocystis jirovecii (*carinii)* pneumonia (PJP) represented the most common indication for ICU admission and mechanical ventilation in patients with HIV/AIDS during this period, accounting for up to 72% of HIV/AIDS patients admitted to ICU (10). The use of mechanical ventilation in this patient population varied from 33% in 1983 and 1984 combined, 0% in 1987, 15% in 1989 and 1% in 1990 (11). This was mostly based on perceived futility of mechanical ventilation for PJP by both physicians and patients (12). Pneumocystis pneumonia was the most common pulmonary disorder in AIDS patients (13). Up to 30% of the patients with PJP had coexisting pulmonary infections. Patients with PJP requiring intubation and ventilation had a very poor prognosis with a patient mortality of up 83% (14).

Brenner et al. (14) evaluated 43 consecutive AIDS patients with pulmonary symptoms and abnormal chest radiographs for *PJP*. No patients received corticosteroids. Thirteen of the patients died, severe abnormalities on initial chest radiographs and alveolar-arterial oxygen difference > 30 mm Hg were associated with higher mortality during the period of treatment for the acute episode (14).

El-Sadr and Simberkoff (15) analysed records of 19 patients with pneumocystis pneumonia who required mechanical ventilation, mortality was 57%.. Most of the nonsurvivors had co-infections which included *Mycobacterium avian intracellulare* and *M. tuberculosis*. The investigators did not comment on the treatment instituted and on whether the other infections were treated (15).

Wachter et al (16) reviewed the medical records of AIDS patients admitted to the ICU for PJP from 1981 to 1985 (Era I) and 1986 to 1988 (Era II). The in-hospital mortality rate in Era I was 86%, compared to 60% in Era II; the major difference between the two time periods was that 74% of patients in Era II received corticosteroids compared to only 5% in Era I. The l-year survival rate among Era II patients was 9%. Of the 6 Era I patients who survived ICU hospitalization, 5 died within 1 year of discharge (16).

In an attempt to identify methods of assessing prognosis in AIDS patients admitted to ICU for PJP-induced acute respiratory failure, Mantaner and coworkers assessed 52 ICU admissions of 51 AIDS patients (17). Forty-seven patients required mechanical ventilation, 34 (72%) died in ICU, 2 more died before hospital discharge. Increased multisystem organ failure (MSOF) score was strongly associated with death from acute respiratory failure due to PJP despite ICU admission. The Acute Lung Injury (ALI) score, and APACHE II were not significantly associated with mortality. 85% of the patients had received adjuvant corticosteroids (17).

Peruzzi et al (18) retrospectively reviewed 29 AIDS patients with PJP admitted to the medical ICU for concurrent lung infections. The incidence of concurrent bacterial lung infection was 7%, compared to 17% in a control group. Overall, 20 of the 29 patients with AIDS and PJP died, however concurrent bacterial infections did not have a significant impact on mortality (18).

The high mortality rate for PJP with respiratory failure continued through the late 1980s to the early 1990s. Staikowsky el al (19) retrospectively reviewed records of 33 patients with AIDS and PJP with acute respiratory failure requiring mechanical ventilation. All the patients were appropriately treated with anti-pneumocystis therapy and corticosteroids. They demonstrated an 81.9% mortality rate with no difference in prognostic factors between the survivors and the non-survivors. However, this study also had a very high ventilator complication rate with 20 cases of pneumothorax; the role of these complications on the mortality rate was not reported (19).

Late in the first decade of the HIV/AIDS epidemic, Hawley et al (20) reported a decline in the frequency of acute respiratory failure secondary to PJP. In a retrospective chart review of 456 episodes of PJP between 1987 and 1991, acute respiratory failure developed in 47 patients (9%). Twenty-seven required mechanical ventilation, of whom 24 died. Despite the decreasing frequency of acute respiratory failure in AIDS-related PJP, intensive care outcomes remained dismal. The lower frequency of both acute respiratory failure and need for mechanical ventilation were attributed to the early use of corticosteroids (20).

Torres and colleagues (21) assessed 42 HIV/AIDS patients admitted to a respiratory ICU because of acute respiratory failure and lung infiltrates. Twenty-eight (67%) had PJP, 14 (31%) of the patients had polymicrobial infection, 7 had both. The mortality rate was higher in PJP patients (18/28 versus 5/14), in patients that required mechanical ventilation, and where there more than 3 days between hospital and ICU admission (21). Nineteen (45%) patients were discharged alive from the ICU. The median survival times were 49 days for the PJP population versus 154 days for other etiologies of respiratory failure (21).

De Palo et al (22) studied 65 consecutive patients with HIV admitted to a medical ICU to determine the outcome of ICU for different illnesses in this patient population. Respiratory failure accounted for 35 patients, 23 of which were secondary to PJP. Sixteen of the patients with PJP were mechanically ventilated, 81% of these died. Mechanical ventilation was required in 23 with respiratory failure with a mortality rate of 79%. These included bacterial pneumonia (6), pulmonary tuberculosis (3), ARDS (2), and pulmonary Kaposi's sarcoma (1). Other causes for admission included sepsis syndrome (10, 5 died), neurologic diseases (8, 3 died), and dilated cardiomyopathy (4, 1 died). Overall mortality was 51% - low CD4 count, respiratory failure and need for mechanical ventilation were associated with a higher mortality rate (22).

In a multicenter prospective study, Rosen et al (23) followed up 1,130 adult patients with HIV to determine ICU admission rates and diagnosis. After 4,298 person-years of follow-up there were 1,361 hospital admissions and 68 ICU admissions. Twenty-four (35%) of the ICU admissions were for pulmonary diseases, 11 had PJP of whom 6 died. Twenty-five of the patients admitted to ICU died, mortality was higher in patients with pulmonary diseases (67% versus 20%). 16 of 28 patients requiring mechanical ventilation died. However, patients with previous AIDS-defining illnesses were excluded, which might account for the lower overall mortality rate and the lower number of cases with PJP (23).

To determine predictors of short-term and long-term survival in HIV-infected patients admitted to ICU, Casalino et al (24) prospectively studied 354 HIV-infected patients admitted to their ICU. Two hundred and eighty patients had AIDS, 131 had a first AIDS-defining illness as the reason for ICU admission. Respiratory illnesses represented the majority of cases (49.2%) followed by neurological illnesses (26.8%). PJP accounted for 45% and bacterial pneumonia for 47% of admissions. Toxoplasma encephalitis was the leading neurological illness, being responsible for 16.6% of all HIV-related ICU admissions. The ICU mortality rate was 20.6%; respiratory illness mortality was 16.7%, neurological illness 23.2%, heart failure 25% and severe sepsis 38%. Mechanical ventilation, duration of mechanical ventilation, percent weight loss, and a higher SAPS I score were significantly associated with higher ICU mortality. These factors were also associated with a high hospital mortality rate of 39%. PJP represented a smaller proportion in this study compared to previous work, but a constant theme was maintained in which mechanical ventilation for PJP was associated with a higher mortality rate (40% versus 5.1%) (24).

1995 – 2004 (Table 2)

During this period, corticosteroids were generally used for PJP and ART was becoming more universally available. The prevalence of PJP was lower, and ICU admission was generally for other opportunistic infections as well as incidental conditions.

Gill et al (25) retrospectively studied 127 HIV-positive patients admitted to ICU in multiple centers in Britain. Of the 94 patients with an HIV diagnoses made prior to ICU admission, 56 had a prior AIDS diagnosis and only 23 (24%) were on ART. Median CD4 count was 40. Respiratory support accounted for 54.1% of indications for ICU admission. This cohort had an ICU mortality of 33% and a hospital mortality of 56%. Mechanical ventilation, CD4 count < 100 cell/mL, previous AIDS diagnosis and PJP were associated with higher ICU and hospital mortality (25).

Afessa and Green (9) prospectively observed 169 ICU admissions of 141 HIV-positive patients from April 1995 to March 1999. Thirty-eight of the 169 admissions were transferred from a medical or surgical ward, mortality was 47%; 131 were admitted from the emergency department with mortality 24%. Overall hospital mortality was 29.6%. Patients with CD4 count > 200 had a lower mortality rate than those with a CD4 less than 200 (22.2% versus 32.8%). Respiratory failure was the most common reason for admission to ICU, with bacterial pneumonia more common than PJP. There was no mortality difference between

causes of pneumonia or for respiratory failure compared to other reasons for admission. Mechanical ventilation was required in 91 (54%) of all ICU admissions, hospital mortality rate was 48%. There was no difference in mortality between those mechanically ventilated for a respiratory disorder and for non-respiratory disorders. Development of ARDS was associated with a high mortality rate. Systemic inflammatory response syndrome (SIRS) developed in 126 (75%), this was associated with a higher mortality (37% vs. 9%). Sepsis was the common cause of SIRS and the lungs were the major site of infection. Severe sepsis and septic shock were associated with a high hospital mortality rate. Non-survivors in this study had a median of 4 organ failures compared to 1 in survivors (9).

A chart review by Morris et al (26) examined 354 HIV-positive ICU admissions, average survival to hospital discharge was 71%. The use of ART increased with time, 4% of patients using ART in 1996 and 32.4% in 1999. Approximately 25% of patients were receiving ART at the time of ICU admission and these were more likely to survive to hospital discharge. ICU admission rates were unchanged in the ART era compared to the pre-ART era. Respiratory failure was the indication for ICU admission in 40% of the patients, and only 10% of the patients were admitted for PJP. The majority of ICU admissions (63%) were non-AIDS related. Survival was not related to CD4 count or HIV viral RNA level. ICU admission for non-AIDS related diagnoses and low APACHE II were highly predictive of improved hospital survival. Patients with AIDS-defining illnesses at the time of ICU admission had a poor survival, irrespective of whether they received ART at the time of ICU admission. PJP, mechanical ventilation and PJP-related pneumothorax were associated with a poor prognosis (26).

In a single centre prospective study, Casalino and colleagues (27) investigated the impact of ART on ICU admission and survival patterns between January 1995 and June 1999. The ART era saw no decline in ICU admissions although there were fewer AIDS-related admissions. 40% of the patients were unaware of their HIV status before ICU admission, and more than 50% of patients were not receiving ART in both time periods. ICU mortality rate was 23%; ICU survivors were more likely to have been on ART, to have had no prior AIDS-related illness, and to have a lower SAPS II score. One- and two-year survival after ICU discharge was 85.3% and 70.8% respectively. The use of ART, HIV stage, presence of AIDS prior to ICU admission and AIDS-related illness predicted long-term outcome (27).

In another single centre prospective study, Narasimhan and others compared HIV-positive patients admitted to their ICU in 2001 (post-ART) with HIV-positive patients admitted to the same unit between November 1991 and October 1992 (pre-ART). 48% of the patients

admitted to ICU in the ART era had not received ART. PJP was present in 3% compared to 34% pre-ART. Most of the patients in the ART era were admitted for HIV-unrelated disorders. Survival to hospital discharge was higher in the ART era (71% vs. 49%). Unlike the previous study, there was no association between the use of ART and survival. More patients received mechanical ventilation in the ART era but patient survival was improved (28).

A similar lack of benefit from prior ART use in patients was shown by Benoit et al (29). More patients were on ART prior to ICU admission in the ART era compared to the pre-ART era (119/236 vs. 5/189). 28% were newly diagnosed with HIV during ICU admission in the ART era compared to 19.6% in the pre-ART era. There was no ICU mortality difference between the two periods (25% versus 27%). Use of inotropes, mechanical ventilation, PJP, pneumothorax and higher SAPS II predicted higher ICU mortality (29).

In a retrospective chart review, Khouli et al (8) assessed the outcomes of critically ill HIV-infected patients admitted to ICU in the era of ART. Over a 3-year period, there were 3902 hospital admission of HIV-positive patients, 273 (7%) of these patients were admitted to ICU (8). Just under half (48%) of the ICU admissions were receiving ART prior to ICU admission. ICU and hospital mortality were 30% and 39% respectively. Use of ART prior to ICU admission was not associated with improved ICU mortality, hospital mortality or decreased length of hospital stay. Pulmonary diagnoses were the most common diagnoses at ICU admission (30%), with a mortality rate of 49% compared to 35% for non-pulmonary diagnoses. Sepsis and neurological diseases had mortality rates of 50% and 48% respectively. Thirty-four patients were admitted for PJP with a mortality of 53%, however 17 of the 20 (85%) who required mechanical ventilation died (8).

Palacios and colleagues (30) reported similar findings. 42% of patients were not aware of their HIV status prior to ICU admission; these patients were more immunocompromised and more likely to be admitted for PJP. Only 30% of the patients admitted to ICU in the ART era were receiving ART and 40% of these were admitted for HIV-related illnesses. There was an overall hospital mortality rate of 53% (30).

Some authors have hypothesized that the mortality of HIV-positive patients admitted to ICU may be decreasing irrespective of the use of ART. Miller et al (31) retrospectively studied 59 HIV-positive patients admitted to ICU for PJP between November 1990 and October 2005. More than half the patients were newly diagnosed with HIV during the index admission. None of the patients were receiving ART and only 15% were receiving *Pneumocystis*

prophylaxis prior to ICU admission. The authors report an ICU mortality rate of 44% and an overall mortality of 53%. Factors that were identified to be associated with a high mortality rate were mechanical ventilation and the development of a pneumothorax (31).

HIV-positive individuals are at increased risk of respiratory illnesses, with 8 times the risk of bacterial pneumonia when compared to HIV-negative individuals (32). In one study, up to 22% of HIV positive patients presented with acute lung injury requiring mechanical ventilation (33). Mechanical ventilation protocols have changed over time, with evidence from the Acute Respiratory Distress Syndrome Network (ARDSNet) advocating lung protective ventilation (34) - could this have affected the change in mortality in HIV positive patients with acute lung injury? Davis and colleagues (33) assessed the effect of low tidal volume ventilation on mortality in HIV-positive patients with acute lung injury admitted to ICU; patient were divided into two time periods, pre-ARDSNet (before 2000) and post-ARDSNet (after 2000). Of 685 HIV-positive patients admitted to ICU from 1996 to 2004, 148 (22%) had acute lung injury, 74 admitted pre-ARDSNet and 74 post-ARDSNet. The aetiology of the acute lung injury in both groups were PJP (34%), non-Pneumocystis pneumonia (38%), sepsis (15%), and aspiration pneumonitis (7%). Lung protective ventilation did not significantly improve outcome (33).

In a study by Barbier and coworkers (35) to determine the aetiology of acute respiratory failure in HIV-infected patients admitted to an ICU, HIV-infected patients accounted for 5% of all ICU admissions; 147 (54.6%) were admitted with acute respiratory failure. Bacterial pneumonia was most common (50.3%), followed by PJP (35.4%). Two-thirds of the patients with PJP were newly diagnosed with HIV infection. 22% of patients in this cohort had two or more causes of acute respiratory failure; bacterial pneumonia was present with PJP in 9 and other opportunistic infections in 8 patients. Overall mortality was 19.7%. Factors associated with increased mortality were invasive mechanical ventilation, use of vasopressors, increased time from hospital admission to ICU transfer and increasing number of causes of acute respiratory failure. Of note, the CD4 count, HIV viral load, and use of ART did not predict mortality (35).

In study by Boonsarngsuk et al, HIV-associated PJP with acute respiratory failure had a higher mortality rate in the first 7 days of ICU treatment, when compared to non-HIV associated PJP (14% vs. 0%), and the overall mortality was higher in the HIV-associated *Pneumocystis* group (36).

In a recent study by Powell et al (37), respiratory failure was responsible for 42% of all ICU

admissions in HIV-infected patients, PJP was the most frequent cause of respiratory failure (28%). In this study, the use of ART was not protective against respiratory failure, with 40% of patients with respiratory failure being on ART, and 42% not on ART. Sepsis was the second most common indication for ICU admission. The incidence of respiratory failure as the cause of ICU admission decreased 52% to 34% between 2000 and 2004. PJP had also decreased from 24% to 9%. Poor outcomes were associated with mechanical ventilation, respiratory failure as the ICU admission diagnosis and PJP. Higher serum albumin and low APACHE II score were associated with survival to hospital discharge (37).

In a retrospective study by Dickson et al (38), 102 HIV-positive patients were admitted; 48% had lower respiratory tract infection, 14% had a neurological illness. HIV-related diagnoses accounted for 67% of ICU admissions; these patients were more immunosuppressed with lower CD4 counts, and less likely to be on ART but had similar APACHE II, identical need for mechanical ventilation and a similar rate of survival to ICU and hospital discharge when compared to those admitted for non-HIV-related diagnoses. Only 37% of patients were on ART on ICU admission, but this did not affect outcome. HIV-infected patients had similar rates of ICU and hospital survival compared to general medical patients. 30% of patients had a new diagnosis of HIV; these patients had a lower CD4 count and were more likely to present with PJP (38).

There are few studies that report outcomes of HIV-infected patients admitted to ICU from developing or low income countries. A study from Mexico by Vargas-Infante and coworkers (39), reviewed ICU admissions of HIV-positive patients from 1985 to 2006. Most patients in this study had AIDS (88%) and 31% of the patients were newly diagnosed with HIV. ICU admission was for mechanical ventilation in 77% and septic shock in 23%. ICU outcomes improved with the advent of ART, 28% of patients received ART in this study. Septic shock and an APACHE II score greater than 13 were associated with death in ICU (39). Similarly, in a study from Brazil by Croda et al (40), 278 HIV-infected patients admitted to ICU were retrospectively reviewed; 38% of the patients were newly diagnosed with HIV at the time of ICU admission, with 80.6% presenting with an AIDS-defining illness and a low CD4 count. Respiratory failure (33.1%) and sepsis (31.3%) were the most common indications for ICU admission. The majority of patients required mechanical ventilation (75.2%) and the use of vasopressors (61%). The ICU mortality rate was 55.4%, and the 6-month mortality rate was 69.4%. Factors associated with poor prognosis were identified as sepsis as the main indication for ICU admission, APACHE II > 19, serum albumin <20, mechanical ventilation within the first 24 hours of ICU admission. The use of ART prior to ICU admission was not protective but there was a reduction in mortality in those started on ART in ICU (40)

2005- 2013 (Table 3)

This period is typified by widespread ART use, with more frequent admission for non-HIV-related causes, but also admissions for complications of and resistance to ART. A considerable number of ICU admissions were still for individuals who were unaware that they had HIV infection.

In a study by Mrus and colleagues (41), HIV/AIDS accounted for 10.3% of severe sepsis cases admitted to hospital. Patients with severe sepsis and HIV/AIDS were less likely to be admitted to ICU compared to those without HIV/AIDS, although those with HIV/AIDS had a higher mortality (41, 42). In their cohort of 88 HIV-infected patients admitted to ICU, Japiassu et al (42) demonstrated that severe sepsis at ICU admission or during ICU stay occurs in 50% of patients. Ward stay prior to ICU admission was associated with increased risk for sepsis, although CD4 count was not a risk factor. The lungs were the major source of sepsis (52%), followed by bacteraemia and venous catheter-related infections, representing 38% and 7% respectively of all sources of sepsis. The majority of infections were nosocomial. In this study, there was a 49% in-hospital mortality rate; the presence of sepsis increased the risk of 28 day mortality by 4 times and the 6 month mortality by 3 times (42).

Greenberg et al (43) showed that a majority of infections in HIV infected patients requiring ICU for severe sepsis were nosocomial or health care-associated, followed by AIDS-related infections. Patients with nosocomial and AIDS-related infections had lower CD4 counts and were less likely to be receiving ART. In this cohort, the respiratory tract was the major site of infection followed by blood stream infections. The in-hospital mortality rate was 42%; death was associated with a higher APACHE II and SOFA score, need for mechanical ventilation and vasopressor support (43).

Chaing et al (44) retrospectively studied the aetiologic and prognostic factors of ICU admission in HIV-infected patients. In this study, respiratory failure was responsible for 44.4% of ICU admissions and sepsis for 33.3%. ICU mortality was 37% and hospital mortality was 48.9%; predictors of hospital mortality were a low CD4 count, admission diagnosis of sepsis and an interval of more than 24 hours between hospital admission and ICU transfers (44).

The advent of ART ushered a new era in the management of HIV-positive patients, with improving outcomes of the general HIV-infected patient population (4). Adlakha and

colleagues (45) studied the survival of HIV-infected patients admitted to ICU in the era of ART; Respiratory illnesses remained the major condition requiring ICU admission with ICU and hospital survival of 74% and 58% respectively. Acute lung injury was present in 79% of those with respiratory illness; PJP and bacterial pneumonia were the major causes of acute lung injury. Respiratory illness requiring mechanical ventilation were associated with poor outcomes, with ICU and hospital survival of 66% and 62% respectively, compared to 93% and 82% for patients with respiratory illness not requiring mechanical ventilation. Just more than half (51%) of the patients in this cohort had an HIV-related admission, this group had ICU and hospital survival of 73% and 70% respectively, significantly lower than the group with non-HIV-related ICU admissions. 55 % of patients were receiving ART at the time of ICU admission; the use of ART was associated with a trend to higher ICU survival and significantly higher hospital survival, the APACHE II score was similar in the two groups. Forty-two (22%) patients were newly diagnosed with HIV during the index admission, half of these patients had PJP.

Van Lelyveld et al studied the short term and long term outcomes of HIV-infected patients in the ART era (46); 52% of patients in this cohort were admitted to ICU for an AIDS-related diagnosis. Only 36% were receiving ART at the time of ICU admission. Overall ICU and hospital mortality were 37% and 50% respectively, with a decrease in both ICU and hospital mortality in the ART era. This study also highlighted a 1 year and 5 year mortality of 53% and 68% respectively in the ART era; this was a significant improvement from 71% and 87% in the pre-ART era. Paradoxically, the group receiving ART had a higher ICU, hospital, 1-year and 5-year mortality compared to the group not on ART. The ART era also ushered in improved outcomes in patients with PJP. Older age, APACHE II > 20 and use of mechanical ventilation were predictors of poor outcomes (46). In contrast, Amancio et al (47) reported ICU and hospital mortality of 46% and 68% respectively and 2 year survival of 38%. Of note in Amancio's cohort, 56% of patients were diagnosed with HIV within a year of admission to ICU and 92% of the patients were admitted with an AIDS-defining condition (47). In a French study by Morquin et al (48), HIV infected patients admitted to ICU had an ICU mortality of 36.7% but only 34.7% were alive at one year post-ICU discharge. ICU mortality was associated with the use of vasopressors, use of mechanical ventilation and higher APACHE II and SAPS II scores. CD4 count, HIV diagnosis, HIV viral load, the use of ART and reason for ICU admission were not significantly associated with mortality (48).

Bhagwanjee and colleagues reported no statistically significant deference in ICU mortality (29% vs. 24%; odds ratio 1.45; 95% confidence interval 0.75-2.80) and hospital mortality (3% vs.6%; odds ratio not calculated) for HIV infected patients compared to HIV uninfected patients admitted to a Durban Tertiary hospital in South Africa (49). This study was limited by the small number of HIV infected patients studied (52), the inclusion of pediatric patients (4% of the HIV infected patients) and the absence of the diagnoses at admission. HIV infected patients suffered more ICU complications but this did not affect mortality. In a prospective study by Edge and collogues 5% (33/661) of patients tested for HIV admitted to the adult burns unit were HIV infected (50). Edge and colleagues reported a Hospital mortality rate of 27%, this was comparable to age and sex matched HIV uninfected control group (24%). There was no report on prior use of ART, opportunistic infection prophylaxis and the stage of HIV infection by CD4 count or clinically. The study by Edge and colleagues is a tertiary care unit study (Tygerburg Hospital, Cape Town), does not reflect outcomes at other levels of care in the same country.

In a South African tertiary care unit (Groote Schuur, Cape Town), Arendse and collogues reported a 41% (48/117) hospital mortality rate in HIV infected patients requiring haemodialysis for acute kidney injury (51). A serum creatinine more than 1230 μmol/l, HIV associated nephropathy and other causes of acute kidney injury other than acute tubular necrosis were the predictors of mortality. The authers did not report whether the patients received care in ICU or not. Patients that did not receive haemodialysis where exclude.

HIV infected patients accounted for 8.4% of ICU patients with *Acinetobacter baumannii* infection or colonization in a retrospective study by Ntusi and colleagues (52). These patients where more likely to have lower CD_4 counts, higher APACHE II and multiple organ dysfunctions syndrome. These variables reflect severity of illness rather than HIV specific findings. The authors did not report on the mortality of the HIV infected patients in this study.

African studies of HIV infected adults in ICU are limited by few patients numbers studied, they are mostly done in tertiary care centers and do not reflect the standard of care in rural and semi urban areas where the standard of ICU is less than ideal.

Studies done in the paediatric population are beyond the scope of this review.

Summary

Progress in the management of HIV and its manifestations has been gradual. There has been a decrease in ICU mortality of HIV infected patients over time. These improvements are attributed to the advent of ART, improved ICU care, decreased incidence of PJP in ICU and improved diagnostic strategies and use of prophylaxis against opportunistic infection in the HIV infected patient population.

This review demonstrates the paucity of data from the developing world, where access to ART, ICU and prophylaxis against opportunistic infection like PJP is limited. Furthermore, there is very limited data on long-term outcomes and functional status beyond the ICU and hospital discharge. There is a need for high quality research from developing world further illuminate our understanding of the relationship between HIV and ICU that is deeply intertwined with access to and use of resources.

1.1.4 **Tables**

1.1.4.1.1 Table 1: Summary of studies from 1981 to 1995

Author	Type of study	Study period	Number of patients	Patients that Died in hospital (%)
Brenner et al., 1987 (14)	Observational	1983 -1986	43	13 (30%)
El-Sadr and Simberkoff 1988 (15)	Retrospective	1982- 1986	19	11(57%)
Wachter et al., 1991 (16)	Retrospective	1981-1985	42	36 (86%)
		1986-1988	35	21 (60%)
Montaner et al., 1992 (17)	Observational	1985- 1991	51	37(72%)
Peruzzi et al., 1992 (18)	Retrospective	1985-1989	29	20(69%)
Staikowsky et al. 1992 (19)	Retrospective	1987-1992	33	27 (81.9%)
Hawley et al. 1994 (20)	Retrospective	1987- 1991	27	25 (92.5%)
Torres et al. 1995 (21)	Prospective	1985 - 1992	42	23 (55%)
De Palo et al. 1995 (22)	Observational	1991-1992	65	33 (51%)
Rosen et al. 1997 (23)	Prospective	1988-1994	63	25 (40%)
Casalino et al. 1998 (24)	Prospective	1990-1992	354	138 (39%)

Table 2: Summary of studies from 1995 to 2005: * denotes ICU mortality.

Author	Type of Study	Study Period	Number of Patients	Patients that Died in hospital (%)
Gill et al. 1999 (25)	Retrospective	1993-1997	127	74 (56%)
Afessa and Green .2000 (9)	Observational	1995-1999	141 (169 ICU admissions)	50 (29.6%)
Morris et al.2002 (26)	Retrospective	1996 -1999	295	29%
Casalimo et al.2004 (27)	Prospective	1995-1999	426	98 (23%) *
Narasimhan et al. 2004 (28)	Prospective	2001	53 (63 ICU admissions)	18 (29%)
Benoit et al. 2004 (29)	Observational	1995-1996 pre-HAART era	189	51(27%)*
		1998-2000 HAART era	236	60(25%)*
Khouli et al. 2005 (8)	Retrospective	1997-1999	259	102 (39%)
Palacios et al 2006 (30)	Retrospective	1990-2003	66	35(53%)
Miller et al. 2006 (31)	Retrospective	1990-2005	59	32(53%)
Dickson et al 2007 (38)	Retrospective	1999-2005	102	31(32%)
Vargas-Infante et al 2007 (39)	Retrospective	1985-1992	16	14 (87%) *
		1993-1996	21	15 (71%)
		1996-2006	53	23(43%)
Davis et al 2008 (33)	Retrospective	1996-2000	74	(59%)
		2000-2004	74	(54%)
Barbier et al 2009 (35)	Retrospective	1996-2000	43	20.9%
		2001-2003	41	19.5%
		2004-2006	63	19%
Croda et al 2009 (40)		1996-2006	278	(55.4%)*
Powell et al 2009 (37)		2000	50	42% *
		2001	52	40%
		2002	75	29%
		2003	66	23%
		2004	68	25%
		Overall	311	31%

1.1.4.1.3   Table 3: Summary of studies from 2005 to 2013: * denotes ICU mortality.

Author	Study type	Study period	Number of patients	Patients that died in hospital (%)
Japiassu et al 2010 (42)	Prospective	2006-2008	88	43(49%)
Chiang et al 2011 (44)	Retrospective	2001-2010	135	66(48.9%)
Yoon et al 2011 (53)	Retrospective	2005-2008	177	60(34%)
Adlakha et al 2011 (45)	Retrospective	1999-2009	192	58(30%)
Van lelyveld et al 2011 (46)	Retrospective	1990-1996 1996-2008	47 82	28(60%) 36(45%)
Amancio et al 2012(47)	Retrospective	2006	125	85(68%)
Morquin et al 2012 (48)	Retrospective	1997-2008	98	37(36.7%)*

1.1.4.1.4   Table 4: Summary of African studies: *denotes ICU mortality.

Author	Study type	Time period	Number of patients	Patients that died in hospital (%)
Bhagwanjee et al 1997 (49)	Prospective	1993 - 1994	52	15 (29%)[#]
Edge et al 2001 (50)	Prospective	1996 - 1999	32	9 (27%)
Arendse et al 2011 (51)	Retrospective	2002 - 2007	117	48 (41%)
Ntusi et al 2012 (52)	Retrospective	2008	21	Not reported

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1.2   **Chapter 2**

<u>HIV-Infected Patients in the Intensive Care Unit - A Retrospective Audit</u>

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1.2.1   **Abstract**

Background:

The indications for and outcomes of intensive care unit (ICU) admission of HIV-infected patients in resource-poor settings like Sub-Saharan Africa are unknown.

Methods:

We reviewed case records of HIV-infected patients admitted to the medical and surgical ICUs at Groote Schuur Hospital, South Africa from 1 January 2012 to 31 December 2012. HIV infection was defined as two positive antibody tests.

Results:

Seventy seven HIV-infected patients were admitted to ICU, 2 were younger than 18 years and were excluded from the final analysis. HIV infection was newly diagnosed in 37.3% of the patients admitted during this period. HIV-positive patients had a mean ($\pm$ standard deviation) CD$_4$ count of 293.9×10^6/L $\pm$ 247.2×10^6/L. Respiratory illness accounted for 30.7% of ICU admissions, community-acquired pneumonia was responsible for the majority of the respiratory cases. ICU and hospital mortality was 25.3% and 34.7% respectively. Predictors of ICU mortality included an APACHE II score >13 (Odds Ratio {OR}, 1.4; 95% confidence interval {CI} 1.1-1.7; p value 0.015), receipt of renal replacement therapy (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 renal replacement therapy (OR, 1.9; 95% CI 1.0-3.6; p 0.056), receipt of inotropic support (OR, 2.0; 95% CI 1.4-3.2; p 0.001). Use of highly active antiretroviral therapy, CD4 count, detectable HIV viral load and the diagnoses at ICU admission did not predict ICU or hospital mortality.

Conclusion

Respiratory illnesses remain the main indication for ICU in HIV infected patients. HIV is diagnosed late with patients presenting in dire straits. Receipt of HAART, CD4 count and the diagnoses at ICU admission are not predictors of ICU or hospital mortality, but rather the severity of illness as indicated by a high APACHE II score, multiple organ dysfunction requiring inotropic support and renal replacement.

1.2.2   **Introduction**

Human immunodeficiency virus /acquired immunodeficiency syndrome (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-infected 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 person years in 1997(2) and reportedly 2.1 per 100 person years in 2010(3). Today HIV-infected 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 infected 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-infected 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 suggests that 7 to 12% of HIV-infected patients admitted to hospital are treated in ICU (8, 9).

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

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

The objective of this study was to identify indications for ICU admission and determine factors associated with high ICU and hospital mortality in HIV infected admitted to ICU in resource-limited settings. This will help in determining the appropriateness of offering ICU care to HIV-infected patients and in the appropriate development of policies and planning for allocation of limited resources.

1.2.3   **Methods**

1.2.3.1.1   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) in Cape Town. GSH is a tertiary hospital affiliated to the University of Cape Town (UCT), and is a 867-bed institution with 16 general medicine and general surgery adult ICU beds (excluding the coronary care unit, neurosurgical ICU and the cardiothoracic ICUs). The study was carried out with the approval of GSH and UCT Human Subjects Research Ethics Committee. The need for obtaining informed consent was waived as this was a retrospective study, and no identifying details would be included.

Patients were enrolled in the study if they were older than 18 years of age at the time of ICU admission, known to be HIV infected or were 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 South Africa) records were interrogated for the information of all the patients admitted to ICU during the study period. Patient folders and laboratory records were examined for the HIV tests results done during and prior to the index admission and for patient diagnoses during ICU admission.

1.2.3.1.2   Case definition

Patients were coded as HIV-uninfected if they had a negative HIV test three months prior to the index admission, untested if there was no documented HIV test results in the folder or no recorded HIV test in the National Health Laboratory Services (NHLS) Electronic records. HIV infection was diagnosed by two positive antibody tests.

1.2.3.1.3   Data collection

A standardised form was used to collect demographic information including age, sex, and ethnicity. Further, details of length of ICU and hospital stay, use of mechanical ventilation and inotropic support were 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 (as defined by Kidney Disease Improving Global Outcomes (KDIGO)) on admission to 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).

1.2.3.1.4   Statistical analysis

Data analysis was performed using SPSS (version 20, IBM, Armonk, New York, USA). Normality of data was tested using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± standard deviation (SD) or, where highly skewed, as median (interquartile range); discrete data are presented as numbers (percentages). The chi-square test or Fisher's exact test was utilised to compare discrete data, as appropriate. ANOVA 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-values of less than 0.05 considered significant.

1.2.4   **Results**

From 1 January 2012 to 31 December 2012, 806 patients were admitted to ICU. Of these, 77 patients were HIV-infected, giving an incidence of 9.6 per 100 person years, 2 patients were younger than 18 years and were excluded in the final analysis (Figure 1). Two hundred and thirty seven (29.4%) patients were HIV-uninfected or had tested HIV-negative in the three months prior to ICU admission. The HIV status was unknown for 492 (61.%) patients admitted to ICU.

1.2.4.1.1   Patient demographic and clinical characteristics at admission to ICU

A total of 75 patients were included in the analysis with a mean 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%). CD_4 count was available for 74 of the 75 patients. HIV-positive patients had a mean (± standard deviation) CD_4 count of 293.9×10^6/L ± 247.2×10^6/L. HIV viral load was available for 27 patients; all these patients were receiving HAART at the time of ICU admission. Thirteen of the 27 patients had a detectable HIV viral load. The median HIV viral load was 20,146.5 RNA copies/ml (25th percentile 372.75 and 75th percentile 25,898.75).   More than a third of the patients (37.3%) were newly diagnosed with HIV during the index hospital admission (Table 1)

Thirty-nine (52%) patients were not receiving antiretroviral therapy (ART). The mean duration on HAART was 6.3 ± 17.5 months. No patients were started on antiretroviral therapy during their ICU stay. Patients that were receiving ART were on HAART.

ICU admission occurred after a median of 2 days (25th percentile 1 and 75th percentile 6) in the referring unit; thirty-three (44%) were admitted to ICU within 24 hours of arrival in hospital, 17 (22.7%) between 24 to 72 hours and 25 (33.3%) were admitted 72 hours after hospital arrival (Figure 2). Thirty-one patients (41.3%) were referred to ICU from the general medical wards, 20% from casualty (medical emergency), 16% from the general surgical wards, 12% from the trauma ward and 10.7% from maternity (Table 1). Approximately one third (30.7%) of the patients were admitted to ICU for respiratory illnesses. Fifteen of the patients with respiratory illness had community-acquired pneumonia, four had pulmonary tuberculosis (initially referred to ICU as community-acquired pneumonia) and the other 4 had *Pneumocystis jirovecii* pneumonia. The diagnosis of *Pneumocystis jirovecii* pneumonia was made after ICU admission on the basis of a positive direct fluorescent antibody test (DFAT) for *pneumocystis jirovecii* on tracheal aspirates. Two of the patients diagnosed with *Pneumocystis jirovecii* pneumonia had a new diagnosis of HIV infection. The other two patients with *Pneumocystis jirovecii* pneumonia were known to be HIV infected and were receiving HAART, their CD_4 counts were less than 150 and both had a detectable HIV viral load. Ten patients had pulmonary tuberculosis and were receiving anti-tuberculosis therapy prior to the admission to ICU. Nineteen patients had previous tuberculosis, which had been fully treated.

1.2.4.1.2   Patient clinical characteristics during ICU stay

The majority of patients (90.7%) required mechanical ventilation, and 50.7% required inotropic support. Fifty-five (73.3%) patients had acute kidney injury on admission to ICU. RRT was offered to 24 patients (32%). Patients presented with a mean APACHE II score (± standard deviation) of 21.6 ± 8.4. The median number of days in ICU and in hospital was 4 (25th percentile 2 75th percentile 8) and 16 (25th percentile 9 75th percentile 34) respectively.

1.2.4.1.3   ICU and in-hospital mortality

Nineteen patients (25.3%) died in ICU, 49 (65.3%) were discharged from hospital alive. Use of RRT was significantly associated with in-ICU mortality (OR, 2.2; 95% CI 1.2-4.1; P 0.018) but not in-hospital mortality (OR, 1.9; 95% CI 1.0-3.6; p 0.056) (Table 2). The use of

inotropes in ICU was associated with both in-ICU (OR 2.3; 95% CI 1.6-3.4; P <0.001) and in-hospital mortality (OR, 2.0; 95% CI 1.4-3.2; p 0.001). An APACHE II of more than 13 at ICU admission was also significantly associated with increased in-ICU mortality (OR, 1.4; 95% CI 1.1-1.7; p 0.015) but not in-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 ICU (p=0.075) or in hospital (p=0.191). Factors including CD_4 count, use of HAART, mechanical ventilation, serum albumin and whether the patient is known or newly diagnosed with HIV were not significantly associated with increased ICU or hospital mortality.

1.2.5   **Discussion**

The key findings of our study were firstly, respiratory illnesses remain the major indication for ICU admission in HIV-infected patients; secondly, there was an in-ICU and in-hospital mortality of 25.3% and 34.7% respectively in a South African tertiary hospital setting; thirdly, factors associated with poor short-term outcomes in HIV-infected patients admitted to ICU were the use of RRT, vasopressor support and an APACHE II score of greater than 13. To our knowledge, this is the first study that determines the outcomes of HIV-infected adults admitted to a South African ICU. These results have implications for resource allocation and management of HIV-infected patients requiring ICU care in resource-constrained settings. These results suggest that sicker patients, as suggested by higher APACHE II, patients requiring 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-infected patients that meet the above criteria. Further more, these results support the general criteria for ICU admission used in the South African public sector, which take into account the severity of the clinical presentation and likelihood of 'reversibility of organ dysfunction' (14).

Intensive care for HIV-infected patients had initially been remarkable for high ICU and hospital mortality (15, 16), in keeping with previous reports we report an ICU mortality rate of 25.3% (10, 17, 18). Respiratory illnesses remain the leading diagnoses at ICU admission in HIV-infected patients (9, 10). It has been reported that mechanical ventilation for respiratory illnesses is associated with poor ICU outcomes (9, 19-22). In this South African cohort, respiratory illnesses represented the most common indication for ICU, but were not associated with increased ICU and hospital death. On the contrary, we also did not find an association of mechanical ventilation with ICU and hospital mortality. In a study by Casalino et al, 45% of the patients with respiratory illnesses had *Pneumocystis jirovecii* pneumonia

(22). In the HAART era, the incidence of *Pneumocystis jirovecii* pneumonia in HIV-infected patients admitted to ICU has decreased to between 3 and 9% (10, 11). Up to 50% of HIV infected patients are unaware of HIV status prior to ICU admission (7, 23-25). This patient group is characterized by pronounced immunosuppression and typically admitted with AIDS-related diagnoses like *Pneumocystis jirovecii* pneumonia when compared to patients that are known to be HIV-infected prior to ICU admission (10, 23, 25-27). The frequency of newly diagnosed HIV-infected patients at ICU admission has remained relatively the same in the HAART era as in the pre-HAART era, but the frequency of OI's in ICU has decreased (7, 9). In this report, only 5% of the patients had *Pneumocystis jirovecii* pneumonia. The diagnoses of *Pneumocystis jirovecii pneumonia* was made during their ICU stay. *Pneumocystis jirovecii* pneumonia, the need for mechanical ventilation in *Pneumocystis jirovecii* pneumonia, development of a pneumothorax in *Pneumocystis jirovecii* pneumonia patient and ICU admission for an AIDS-related diagnoses 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-infected patients that might have qualified for ICU care but were not referred to 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 the physician attitudes towards ICU care for HIV-infected patients have changed.

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

Between 24 and 50% of HIV infected patients receive HAART prior to ICU admission (8, 10, 23, 26). Receipt of HAART prior to ICU 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 and others have reported that receipt of HAART did not predict short-term outcomes (7, 8, 11, 27). In this study, 48% of the patients were on HAART prior to ICU admission, 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, either ICU and hospital mortality.

Up to 50% of HIV-infected 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 to for sepsis in HIV-infected patient (32). Severe sepsis has been reported to be associated with poor ICU outcomes in HIV-infected patients (32). In this study, 13.3% of the patient had the diagnoses of severe sepsis at ICU admission, 42% 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% of the patients in this 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-infected patient in ICU (In our hospital, we have adopted lung protective ventilation, surviving sepsis guidelines and appropriate glucose control in our ICU (34, 35)). There were very few case of *Pneumocystis jirovecii* pneumonia, this might account for the apparent lack of association between respiratory illnesses, mechanical ventilation and death.

Our study has several important limitations. Firstly it is a single centre study. Secondly, the study suffers from the limitations and biases of its retrospective nature. Thirdly, 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. Fourthly and most importantly, 61% of our ICU population did not have an HIV test, considering that our community has a high prevalence of HIV infection this may presents a missed opportunity in testing and potential treatment.
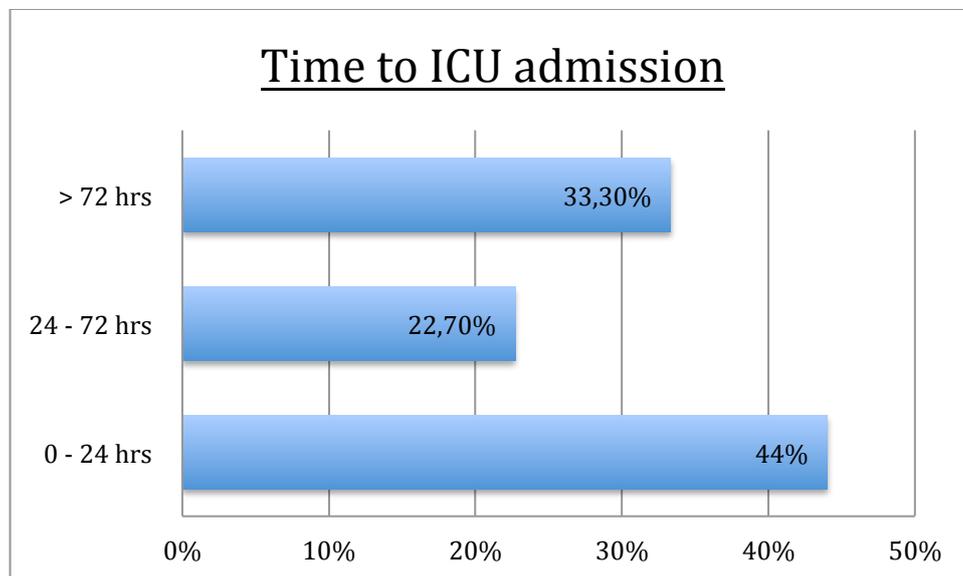
This study shows that critical care outcomes for HIV-infected patients at Groote Schuur Hospital are comparable to those in the developed world. This study presents findings from a tertiary care unit, this findings are not representative of the rest of country. It highlights that ICU outcomes for this patient population depend on the severity of the acute illness irrespective of the receipt of HAART and the immune status. More research is needed that is representative poorer provinces of the country and the rest of the African continent.

1.2.6 **Figures and tables**

1.2.6.1.1 Figure 1: Flow diagram demonstrating patient enrolment. ICU denotes intensive care unit, HIV denotes Human Immunodeficiency Virus.
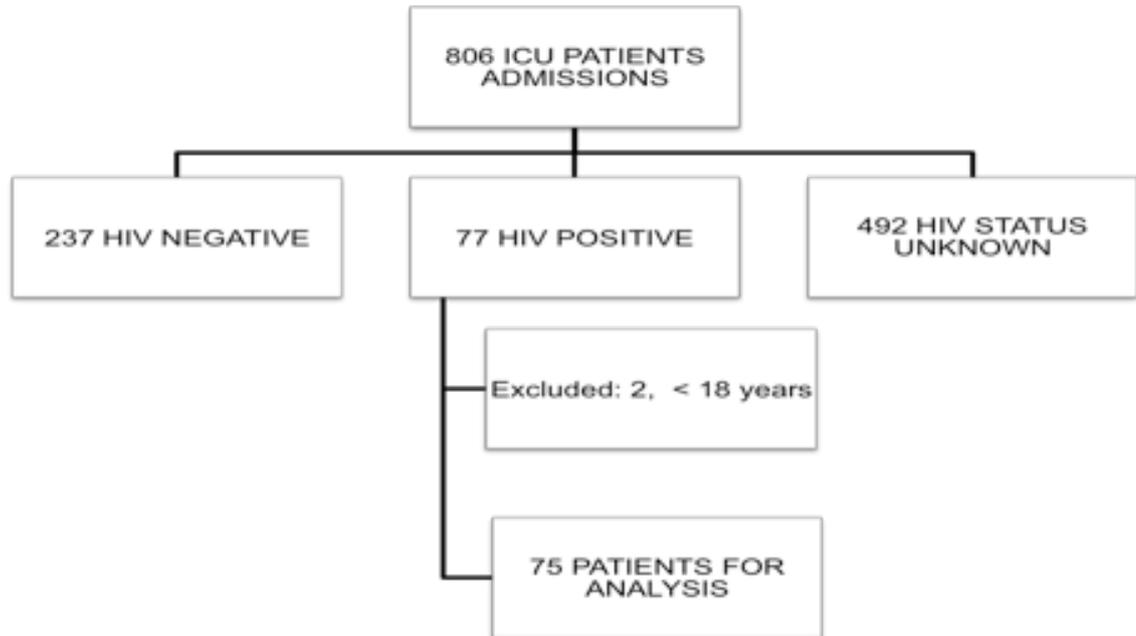
1.2.6.1.2 Figure 2: Number of *days* in the referring unit prior to ICU admission

Characteristic	Number N=75
Age (years)[¶]	36.5 ±9.6
Female (%)	64
Race (%)	
Black	84
Mixed race	16
Newly diagnosed HIV (%)	37.3
On HAART (%)	48
Duration on HAART (months)	0-72 range
CD_4 count ($\times 10^6$/L) [¶]	293.9 ±247.2
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
Medical ward	41.3
Surgical ward	16
Maternity	10.7
Number of days in the referring unit[#]	2 (1 and 45)
Diagnoses at ICU admission (%)	
Respiratory illness	30.7
Severe sepsis	13.3
Trauma	12
Drug toxicity and poisoning	8
Neurological illness	9.3
Elective surgery	8
Other*	18.7
APACHE II [¶]	21.6 ± 8.4
AKI on admission (%)	26.7
Mechanical ventilation (%)	90.7
Renal replacement therapy (%)	32
Inotropic support (%)	50.7
ICU Complications (%)	
AKI	16
Sepsis	25.3
AKI and sepsis	17.3
Number of days in ICU[#]	4 (2 and 8)
Number of days in Hospital[#]	16(9 and 34)

[¶]Mean ± SD
*Included patient admitted with renal illness, malaria, gastrointestinal illness, emergency surgery and cardiac illness.
[#]Median (interquartile range)
[¥] Includes medical emergency (casualty) and trauma unit.

Table 2. Patient outcomes according to specific variables

	Death in ICU	Odds ratio (95% CI)	P value	Death in hospital	Odds ratio (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 (n=35)	12	1.4 (0.9-2.3)	0.183	15	1.5 (0.9-2.3)	0.118
Duration in the referring unit			0.075			0.191
Less than 24 hours (n=33)	9			12		
24 to 72 hours (n=17)	1			3		
More 72 hours (n=25)	9			14		

1.2.7 **References**

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