Outcome of HIV positive patients presenting with renal failure

at Charlotte Maxeke Johannesburg Academic Hospital

DECLARATION

I, Ahmed Ismail Vachiat declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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29 September 2011

DEDICATION

My parents, Ismail and Rashida,

for instilling in me the belief that the best investment is education.

My wife Fatima and son Mohammed,

for their time and love.

PUBLICATIONS AND PRESENTATIONS

Publications

Abstract for the South African Renal Society Congress

Outcome of HIV positive patients presenting with renal failure at Charlotte Maxeke Johannesburg Academic Hospital

Cardiovascular Journal of Africa, 2010, 21:3

Presentations

1. Outcome of HIV positive patients presenting with renal failure at Charlotte Maxeke Johannesburg Academic Hospital

   South African Renal Society (Cape Town)

   18th April 2010

2. Outcome of HIV positive patients presenting with renal failure at Charlotte Maxeke Johannesburg Academic Hospital

   Wits Research Day (Johannesburg)

   22 September 2010

ABSTRACT

Outcome of HIV positive patients presenting with renal failure at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

Background

The majority of the 33.4 million people infected with HIV worldwide reside in sub-Saharan Africa. The HIV prevalence amongst young South Africans (ages 15- 49) is 16%. HIV is the third leading cause of ESRD in African - Americans aged 20-64 in the United States. There is a paucity of data regarding the prevalence of acute kidney injury (AKI) in HIV patients in sub-Saharan Africa.

Methods

A retrospective review of 101 HIV positive patients presenting with renal failure at the CMJAH from 1st October 2005 until 31st October 2006 was undertaken. There were 50 HIV positive patients with presumed AKI that were compared to 90 HIV negative patients with AKI.

Results

A total of 684 patients presented with renal failure, 101(14.8%) of whom were HIV positive. Ninety-nine of the HIV positive patients were black and 56 were male. The mean age of HIV positive patients with renal failure was 38 years. Fifty-seven patients presented with AKI (seven patients were excluded due to lack of records), 21 with acute on chronic renal failure and 23 with chronic renal failure. The causes of AKI in the HIV positive group included sepsis (62%), haemodynamic instability (20%), toxins (10%), urological obstruction (8%) and miscellaneous (10%).

The common underlying aetiologies of the 90 HIV negative patients studied presenting with AKI were sepsis (43%), haemodynamic instability (17%), toxins (7%), urological obstruction (8%) and

miscellaneous (23%). Forty-seven (52%) of these HIV negative patients recovered. Forty-two (47%) patients died, compared with 22 (44%) patients in the HIV positive group.

Hyponatraemia, hyperkalaemia, hypochloraemia and acidosis were more common in the HIV positive patients. Dialysis was initiated in 36% of HIV positive patients with AKI. There were more HIV positive patients that recovered with supportive care, including fluid therapy when compared to HIV negative patients. Recovery was noted to be more rapid in the HIV positive group. Using survival and death as the outcome there was no difference between the HIV positive and the HIV negative group presenting with AKI ($p<0.7173$).

Discussion

HIV positive patients presented with renal failure at a younger age – a mean age of 38 years in this study. Previous studies have shown mean ages ranging from 35 years to 46.7 years. The majority of the HIV positive patients presenting with renal failure were black (98%). The racial predominance is different to that of other countries which might be due to epidemiological factors. The gender differences were similar when compared to other studies. Sepsis was the more common aetiological factor of AKI (62% of HIV positive patients compared to 43% of HIV negative patients). HIV positive patients with AKI presented at an advanced stage of immunosuppression (more than 50% had CD_4<100cells/µl). Electrolyte disturbances were common in HIV positive patients with AKI.

Conclusion

HIV positive patients with AKI presented with advanced immunosuppression. Sepsis was the most common aetiology of AKI. Supportive management or renal replacement therapy resulted in recovery in a large number of patients.HIV positive patients should be treated acutely just as HIV negative patients and should not be excluded on the basis of their HIV status. Dialysis should be

offered when indicated and aggressive fluid resuscitation should be emphasized. Outcomes were similar in HIV positive and HIV negative patients presenting with AKI.

ACKNOWLEDGEMENTS

My teacher, supervisor and mentor Professor S. Naicker, Academic Head of Internal Medicine and Head of Nephrology at the University of Witwatersrand. I started thinking about this project during my Community Service year and during my registrar time went through the different processes in order to complete the MMed. Professor S. Naicker is undoubtedly passionate about education.

Dr S.Wadee, was my co-supervisor and I am grateful to him for his guidance and support.

I would like to thank the Nephrology staff at the CMJAH especially Drs G. Paget, S. Naidoo and

J.Fabian who were all consultants that helped with patient reviews during my training.

I would also like to thank Mr E. Musenge for assisting with the Statistics and Professor M. Tikly and his wife, Mohsina for their nurturing and encouragement.

And to the patients…Thank you immensely. It is my hope that this research report can bear fruitful and beneficial knowledge.

"Doctors record patient's medical history without paying much attention to the patient. But we must never forget that the look on the patient's face, the tremble in his hands, the falter in his speech, the dreams he has, the drawings he makes, are all potential signs (windows) of what really troubles him."

Sir William Osler

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ABBREVIATIONS

AIDS	Acquired immunodeficiency disease syndrome
AKI	Acute kidney injury
AOCRF	Acute on chronic renal failure
ART	Anti-retroviral therapy
ATN	Acute tubular necrosis
BVF	Biventricular failure
CAP	Community acquired pneumonia
CD_4	Cluster of differentiation
CKD	Chronic kidney disease
Ca	Creatinine (admission)
Cal	Calcium
Cl	Creatininie (lowest)
Cd	Creatinine (discharge)
Cl^-	Chloride
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CONS	Conservative
COPD	Chronic obstructive pulmonary disease
D/C	Discharged
DBP	Diastolic blood pressure
DCMO	Dilated cardiomyopathy
DM	Diabetes mellitus
E+	Erythrocytes present (dipstix)
ERY	Erythrocytes present (laboratory)
ESRD	End stage renal disease
GE	Gastroenteritis
GFR	Glomerular filtration rate
HAART	Highly active anti-retroviral therapy
HB	Haemoglobin
HD	Haemodialysis
HIV	Human immunodeficiency virus
HIVAN	HIV – associated nephropathy
HIVICK	HIV – immune complex kidney disease
HT	Hypertension
HUS	Haemolytic uraemic syndrome
ICU	Intensive Care Unit
K	Potassium
KS	Kaposi's sarcoma
L+	Leucocytes present (dipstix)
LEUK	Leucocytes (laboratory)
MED / M	Medical ward
MHT	Malignant hypertension
MDRD	Modification of Diet in Renal Disease
MISC	Miscellaneous
Mg	Magnesium
MRSA	Methicillin resistant Staphylococcus aureus
Na	Sodium
NIAID	National Institute of Allergy and Infectious Diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NS	Not significant

NSAIDS	Non-steroidal anti-inflammatory drugs
OBS	(urological) Obstruction
O&G	Obstetrics and gynaecology ward
PCP	Pneumocystis carinii (jeroveci) pneumonia
PCR	Protein creatinine ratio
PIH	Pregnancy induced hypertension
PO_4	Phosphate
PROT	Protein (dipstix)
PTB	Pulmonary tuberculosis
RIFLE	'R' = Risk of renal dysfunction, 'I' = Injury to the kidney, 'F' = Failure of kidney function, 'L' = Loss of kidney function, 'E' = End-stage renal disease
RIP	Died
RRT	Renal replacement therapy
RPGN	Rapidly progressive glomerulonephritis
SALM	Salmonella
SBP	Systolic blood pressure
SEMDSA	Society of Endocrinology, Metabolism and Diabetes of South Africa
SIADH	Syndrome of anti-diuretic hormone hypersecretion
SJS	Steven Johnson's syndrome
SLE	Systemic lupus erythematosis
STAPH	Staphylococcus aureus
SURG / S	Surgical ward
TB	Tuberculosis
TTP	Thrombotic thrombocytopaenic purpura
U_E.Coli	Urine (E.Coli)
U_KLEB	Urine (Klebsiella pneumonia)
Ua	Urea (admission)
Ul	Urea (lowest)
Ud	Urea (discharge)
UA	Uric acid
UTI	Urinary tract infection
VBD	Vanishing bile duct
WCC	White cell count
WITS	University of Witwatersrand

PREFACE

Kidney disease is common in HIV positive patients, occurring in 30% of patients, and is a common cause of end-stage renal disease (ESRD) (Gupta et al. 2005). Data on HIV patients with AKI in developing countries is scanty.

This research report is a retrospective review of all patients presenting to the adult renal unit at Charlotte Maxeke Johannesburg Academic Hospital between 1st October 2005 and 31st October 2006. The spectrum of renal disease in HIV positive patients is reviewed. The presentation of renal disease in HIV positive patients, demographic, clinical and laboratory data, dialysis and mortality were evaluated.

INTRODUCTION

1.1 Background and History

The Human Immunodeficiency Virus (HIV) was first identified in 1981 (Gottlieb et al. 1981) and was subsequently reported to affect the kidney (Rao et al. 1984). HIV is a lentivirus (a member of the retrovirus family) that causes the Acquired Immunodeficiency Syndrome (AIDS), which leads to life-threatening opportunistic infections. HIV infects and destroys CD_4 T cells, ultimately leading to the loss of immune control of multiple pathogens and cancers (Douek et al. 2009). HIV associated nephropathy is a common cause of end-stage renal disease (ESRD) (Gupta et al. 2005).

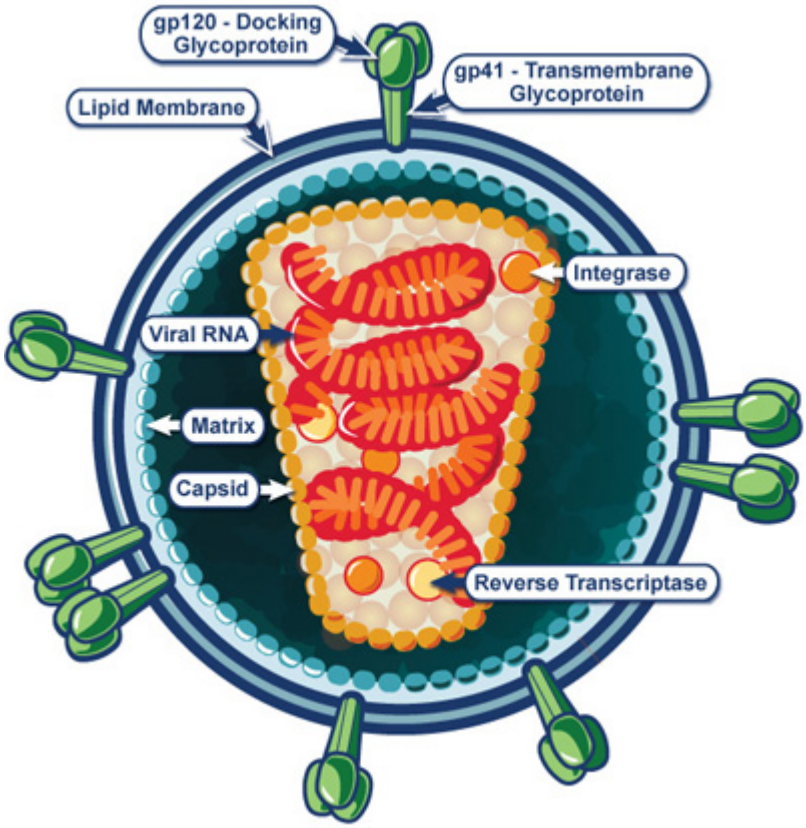

Figure 1 Human Immunodeficiency Virus structure (NIAID 2010)

1.2 **Prevalence of HIV infection in sub-Saharan Africa**

In 2006, sub-Saharan Africa accounted for 72% of all known deaths due to AIDS worldwide. During this period, the population of sub-Saharan Africa was 800 million people (12% of the world's population). Of the 33.4 million people worldwide living with HIV, 22.4 million reside in sub-Saharan Africa. The burden of disease is evident in that sub-Saharan Africa, while having over 10% of the world's population, accounts for more than two-thirds of those infected with HIV (UNAIDS 2009).

The prevalence of HIV infection exceeds 10% in nine countries in Southern Africa. About 1.9 million adults and children became infected with HIV in 2008 and a further 1.4 million deaths were attributable to AIDS. The average life expectancy is below 40 years. Women in South Africa account for 60% of all HIV infections (UNAIDS 2009).

The number of people newly infected with HIV fell from 2.2 million people in 2001, to 1.8 million people in 2009 (see Table 1).With an estimated 5.6 million (5.4 million – 5.8 million) HIV positive people, South Africa continues to have the world's largest HIV epidemic (UNAIDS 2010).

		Adults and children living with HIV	Adults and children newly infected with HIV	% Adult prevalence (15–49 years)	AIDS-related deaths among adults and children
SUB-SAHARAN AFRICA	2009	22.5 million [20.9–24.2 million]	1.8 million [1.6–2.0 million]	5.0 [4.7–5.2]	1.3 million [1.1–1.5 million]
	2001	20.3 million [18.9–21.7 million]	2.2 million [1.9–2.4 million]	5.9 [5.6–6.1]	1.4 million [1.2–1.6 million]

Table 1 Sub-Saharan HIV statistics (UNAIDS 2010)

HIV trends in sub-Saharan Africa

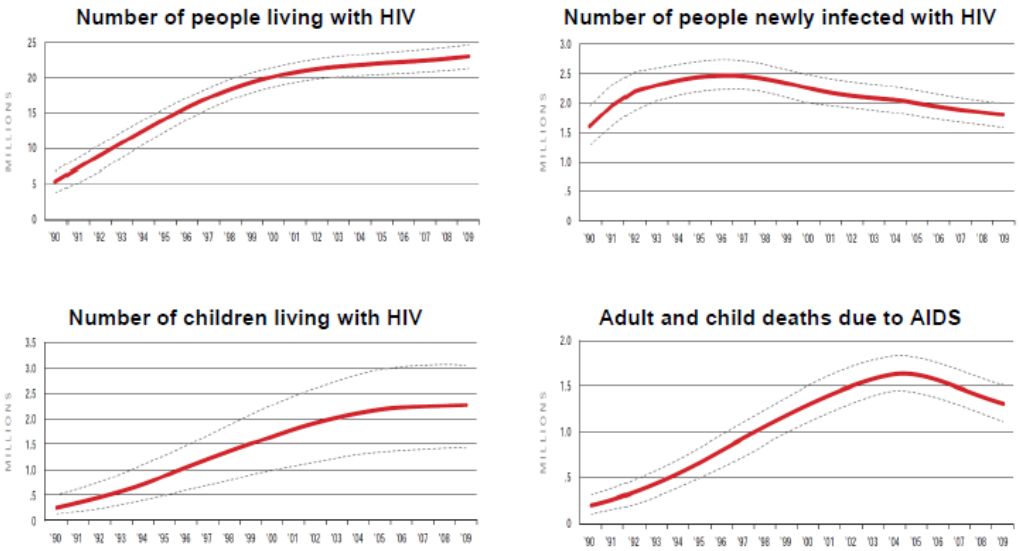

Figure 2 HIV trends in sub-Saharan Africa (UNAIDS 2010)

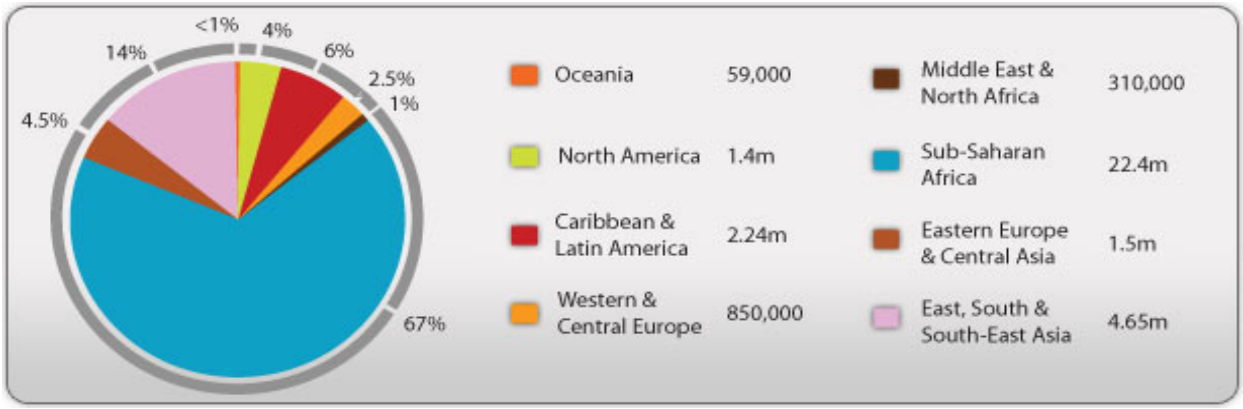

Figure 3 HIV worldwide (UNAIDS 2009)

1.3 Presentation of kidney disease in HIV positive patients

Kidney disease can present as acute kidney injury (AKI), acute on chronic renal failure (AOCRF) and chronic kidney disease (CKD) (Table 2). In the developed nations the spectrum of pathology has changedwith the advent of HAART. Since the advent of HAART, morbidity and mortality from HIV infection has decreased substantially (Palella et al. 1998; Hogg et al. 2001); however HIV positive patients on HAART are susceptible to complications of nephrotoxicity. In sub-Saharan Africa, the majority of patients who are admitted with HIV infection are treatment-naive and present with AKI secondary to pre-renal failure and opportunistic infections.

▪ Electrolyte and acid-base disturbances
▪ Acute Kidney Injury (AKI)
▪ Chronic Kidney Disease (CKD) o HIV-associated glomerulonephropathies o Intrinsic renal disease unrelated to HIV itself (e.g. diabetes mellitus and hypertension)
▪ Acute on Chronic Kidney Disease
▪ Side effects related to treatment of HIV, which include ART and drugs used to treat complications of HIV
▪ Long term metabolic side-effects of ART

Table 2 Spectrum of renal disease in HIV infection

1.4 HIV and Acute Kidney Injury

Acute kidney injury (previously termed acute renal failure) occurs in 5-7% of hospital admissions and affects 30% of HIV positive patients admitted to ICU (Kathleen 2008). Acute kidney injury occurs over hours to days and is characterized by an abrupt decline in GFR, rising blood urea and serum creatinine, the loss of water and salt homeostasis and life-threatening metabolic consequences.

1.4.1 *Definition*

There are many definitions of AKI (more than 30) and the lack of a concise universal definition has made it difficult to compare data and to guide therapy. The Infectious Diseases Society of America defined AKI in HIV- seropositive patients as a serum creatinine level greater than 1.5mg/dL (132.6µmol/L) or a 1.3-fold increase above the laboratory baseline that recovers within 3 months. An international initiative has attempted to come to a consensus regarding the definition of AKI and hence the RIFLE classification (Table 3) was developed (Bellomo et al. 2004). There are three severity categories (risk, injury, loss) and two clinical outcome categories (loss and end stage renal disease). A recent study from London classified patients with AKI using a GFR reduction of 40% from the admission creatinine (Ibrahim et al. 2010).

Class	GFR Criteria	Urine Output criteria
Risk	Serum creatinine X 1.5	<0.5ml/kg/h X 6h
Injury	Serum creatinine X 2	<0.5ml/kg/hr X 12h
Failure	Serum creatinine X 3 or serum creatinine >355umol/L with an acute rise > 44umol/L	<0.3ml/kg/h X 24h or anuria X 12h
Loss	Persistent acute renal failure > 4 weeks	
ESRD	End stage renal disease > 3 months	

Table 3 RIFLE criteria (Bellomo et al. 2004)

1.4.2 *Classification*

Acute kidney injury is divided into pre-renal, intra-renal (intrinsic) and post-renal failure (Table 4). Pre-renal failure is the most common presentation and can progress to acute tubular necrosis (ATN), which once developed may be irreversible (Kathleen 2008). Post-renal presentations are frequently reversible, hence the cause of obstruction needs to be appropriately investigated.

Pre-renal	Intra-renal	Post-renal
Hypovolaemia dehydration diarrhoea vomiting haemorrhage Sepsis Heart failure Pancreatitis Renal vasoconstriction NSAIDS	ATN sepsis ischaemia hypotension toxins rhabdomyolysis Drugs: NSAIDS , amphotericin B, tenofovir, contrast, chemotherapy Infection: bacteria: mycobaceria tuberculosis, mycobacteria other than TB (MOTT) viruses: herpes, cytomegalovirus, varicella zoster virus, BK virus fungi : aspergillus, cryptococcus, histoplasmosis, candida, mucormycosis parasites : pneumocystis, toxoplasmosis, microsporia Glomerulopathies HIVAN HIVICK other : IgA, acute post-infectious, lupus nephritis RPGN secondary to rifampicin HUS/TTP Acute Interstitial Nephritis Drugs: NSAIDS, indinavir, bactrim, Tumours renal cell carcinoma, lymphoma multiple myeloma, Kaposi's sarcoma	Obstruction crystalluria high dose bactrim acyclovir nephrolithiasis indinavir atazanavir hyperuricosuria chemotherapy Herpes related neurogenic bladder Prostatic hypertrophy malignancy (men)

Table 4 Classification of AKI in HIV infection (Fabian and Naicker. 2009)

The most common form of renal replacement therapy for HIV positive patients is haemodialysis (Ahuja et al. 2003). For chronic dialysis, the outcomes between haemodialysis and peritoneal dialysis are equivalent (Abbott et al. 2003). Disadvantages of haemodialysis include the risk of needle stick injuries to healthcare providers. Disadvantages of peritoneal dialysis include increased protein losses and a potential for severe peritonitis. For acute dialysis in HIV positive patients, the usual indications apply as for HIV negative individuals (Table 5).

oliguria : urine output < 200ml in 12hours
anuria : urine output < 50ml in 12hours
hyperkalaemia : K > 6,5mmol/L
severe acidosis : pH < 7
azotaemia : urea concentration >30mmol/L
uraemic encephalopathy
uraemic neuropathy/myopathy
uraemic pericarditis
plasma sodium : Na >155mmol/L or <120mmol/L
Hyperthermia
drug overdose with dialyzable toxin

Table 5 Proposed criteria for initiation of RRT in patients with AKI (Lameire et al. 2005)

Acute kidney injury in hospitalized ART-naive HIV positive patients is associated with a six-fold higher risk of in-hospital mortality (Wyatt et al. 2006). In the HIV negative population AKI occurs in about 19% of patients with moderate sepsis, 23% of those with severe sepsis and 51% of those with septic shock when blood cultures are positive (Schrier et al. 2004).

Acute kidney injury incidence rates vary between 0.9% to 20% and mortality rates from 25% to 80% in the HIV negative population (Lameire et al. 2005). The epidemiology of AKI in Africa was reviewed in 2008 (Table 6). Prior to this article there were very few publications about the

incidence of AKI in Africa. A review of causes per region was undertaken and the majority of causes of AKI included infections (HIV and malaria), diarrhoea and nephrotoxins. AKI in Africa is challenging due to the late presentation and a lack of resources (Naicker et al. 2008).

Country	Causes of AKI
North Africa	
Algeria	Toxins, trauma/surgery, urologic
Egypt	Surgical, toxins, obstructive
Morocco	Hemodynamic, sepsis, obstructive
West Africa	
Cameroon	Malaria, obstetric, toxins
Cote d'Ivoire	Malaria, HIV, toxins
Nigeria	Sepsis, obstetric, toxins
Senegal	Obstetric, malaria, herbal toxins
Democratic Republic of Congo	Infections (especially malaria), hypovolemia, toxins
East Africa	
Kenya	Infection, obstetric, surgical
Burundi	Malaria, dehydration (HIV, diarrhea)
Rwanda	Infections, trauma, toxins
Ethiopia	Malaria, surgical, acute glomerulonephritis
Eritrea	Infection
Sudan	Infection, toxins
Southern Africa	
South Africa	Infections (including HIV), toxins, pregnancy
Mozambique	Malaria, dehydration, HIV
Zimbabwe	Prerenal (HIV), malaria, obstetric
Zambia	Malaria, obstetric
Malawi	Diarrheal diseases, malaria, sepsis

Table 6 Causes of AKI in Africa (Naicker et al. 2008)

1.4.3 *International Literature (HIV and AKI)*

Six retrospective studies focusing on HIV and AKI were reviewed (see Appendix 5). Four of these studies reviewed HIV positive hospitalized patients and two studies reviewed ambulatory HIV positive patients with AKI.

In a group of 754 ambulatory HIV positive patients (from the USA) observed between 2000 and 2002, 111 AKI events occurred in 71 subjects; mean age was 40 years and 61% were black. AKI was more common in men (68%), in those with CD4<200cells/mm³ and HIV RNA levels >10 000 copies/ml. Diarrhoea, nausea and vomiting, liver failure and infections were the most common causes of pre-renal failure occurring in 38% of patients. AKI not recovering after 24 hours of hydration was defined as acute tubular necrosis (ATN). Those with low CD_4 counts were more likely to develop ATN. Ischaemic or noncontrast drug nephrotoxicity accounted for the majority of intrinsic renal failure (Franceschini et al. 2005).

There were two cases of thrombotic thrombocytopaenic purpura – haemolytic uraemic syndrome (TTP-HUS). Over 50% of all renal events were associated with infections. Drugs associated with AKI included antibiotics (amphotericin B, aminoglycosides, vancomycin) and antiretroviral agents (indinavir, tenofovir and nevirapine). AKI was often seen in patients with AIDS, Hepatitis C and those on HAART. About one-quarter of the patients had hepatitis C virus co-infection. The median CD_4 cell count was over 350cells/µl and about one-third had a CD_4 count <200cells/µl. Repeat episodes of AKI were more frequent in those with advanced HIV disease. Renal replacement therapy was required in 5 patients (Franceschini et al. 2005).

In France, a review over 8.5 years identified 92 hospitalized HIV positive patients with AKI. The mean age was 35 years and 88% were black. Eighty-two % of patients had overt AIDS and the mean CD_4 count at baseline was 76 cells/µl. The mean serum creatinine on admission was 480µmol/L. The common causes of AKI were sepsis (75%), HUS (32%) and ATN (26%). The

mortality rate was 20%. Renal biopsies were performed in 60 patients; HIVAN was present in 23% (Peraldi et al. 1999). This study claimed an academic interest in thrombotic microangiopathy but nevertheless highlights the importance of renal biopsies.

One of the largest registries examined the incidence and predictors of AKI before and after the introduction of HAART in the USA. There were 52 580 HIV infected patients reviewed in 1995 and 25 114 in 2003. In the post-HAART cohort (2003), 1516 (6%) presented with AKI. The mean age was 46.7 years and 54.6% were black. Males accounted for 46.7 % of the patients reviewed. The in-hospital mortality was 26.6%. Acute kidney injury was reported more often during hospitalizations for HIV-infected patients than for uninfected patients in 1995 (2.9% vs 1.0%) and in 2005 (6.0% vs 2.7%) (Wyatt et al. 2006). The problem with observational databases is that the diagnosis of AKI is based on clinical judgment and no laboratory data was reviewed.

The 'RIFLE' criteria was used in a retrospective review of critically ill HIV positive patients from Portugal between 2002 and 2006. Acute kidney injury occurred in 46 patients. Of these, 12 patients (26%) were classified in class 'R', 9 patients (19,5%) were in class 'I', and 25 patients (43%) were in class 'F'. The mean age was 42.7 years and 60% were black. Males accounted for 40% of cases. Sepsis was present in 84% of patients. Two patients presented with thrombotic thrombocytopaenic purpura (TTP). Renal replacement therapy was prescribed for 7 patients. The overall mortality was 43.3% (Lopes et al. 2007).

The outcome of severe acute renal failure in patients with AIDS was reviewed retrospectively over almost a decade at the Renal Division at Kings County Hospital Centre in New York where 146 HIV positive patients (pre-HAART) with a serum creatinine concentration of 530µmol/L or higher were included in the study. This group was compared with a group of 306 HIV negative patients (Table 7). Ninety-one % of the HIV positive patients with AKI were less than 50 years of age

compared with only 33% of the HIV negative patients. Septicaemia was responsible for AKI in 75% of patients in the HIV positive group compared to 39% in the HIV negative group.

Thirty-six % of the HIV positive patients were terminally ill and could not be treated by aggressive dialysis, compared with only 18% in the elderly HIV negative group. Recovery of renal function and mortality were determined by the patient's haemodynamic situation and not by HIV status. The impact of AIDS on AKI was illustrated by the fact that despite being younger, over one third of the patients confined to the intensive care units with multi-organ dysfunction and overwhelming sepsis were considered to be agonal and untreatable. It was also noted that the number of patients seen over the decade increased substantially (Rao et al. 1995).

	HIV positive (%)	HIV negative (%)
No. of patients	146	306
Sex (male/female)	113 / 33	197 / 109
Age mean (years)	38.4	55.2
Aetiology of AKI: Sepsis	76/146 (52)	73/306 (24)
Nephrotoxins	33/146 (23)	45/306 (15)
Miscellaneous	37/146 (25)	53/306 (17)
Urinary obstruction	0/146 (0)	54/306 (17)
No. of agonal patients not dialyzed	53 (36)	57 (18)
Supportive care (no dialysis)	20 (14)	42 (14)
Renal recovery in dialyzed patients	41/73 (56)	98/207 (47)
Overall renal recovery	58/93 (62)	133/249 (53)
Overall mortality	88/146 (60)	173/306 (56)

Table 7 Comparison of AKI in HIV positive and HIV negative patients (Rao et al. 1995)

A recent review from London, has shown that immunodeficiency and renal impairment were risk factors for HIV-associated acute kidney injury. This review of almost a decade (January 1999 to December 2008) found that the incidence of AKI was 2.8 episodes per 100 000 person-years. This study included patients with GFR less than 60ml/min and also included patients if their GFR was reduced by more than 40% from baseline and the duration of the AKI was less than 90 days. There were 2556 patients reviewed and 184 patients (7.2%) experienced AKI. Forty-five percent of the patients were receiving anti-retrovirals. Opportunistic infections were the commonest causes of AKI in patients who had CD_4<50 cells/µl. Death was more common in those patients with AKI compared to those without AKI (32.1 vs 3.7%, p<0.001).There was an increase in the incidence of AKI at lower CD_4 counts and lower glomerular filtration rates. Ethnicity, hepatitis B or C coinfection, exposure to combination antiretroviral therapy with or without indinavir, tenofovir or atazanavir and HIV viraemia were not associated with AKI (Ibrahim et al. 2010).

A retrospective review of 117 HIV patients between 2002 and 2007 (17% on HAART) requiring acute dialysis in Cape Town showed that higher CD_4 counts (OR=0.994), lower pre-dialysis serum creatinine (<1230µmol/l) and longer hospitalization(OR=0.93) significantly increased survival. The median age was 34 years (range 29.0-49.0) with a male predominance (53.8%). The median CD_4 count was 164 cells/mm^3 and 32.5% of subjects had a CD_4 > 200cells/mm^3. A lower mean CD_4 count (132 cells/mm^3) was found for patients who died. The median pre-dialysis creatinine was 988µmol/l (range 729.8-1230.0). HBsAg was positive in four patients. The median period of hospitalization was 15.0 days. Sepsis was present in 50.4% of patients.Forty-eight patients (41%) died. There was a good chance of survival when the diagnosis was ATN and when the CD_4 count was more than 200cells/mm^3(Arendse et al. 2011).

1.5 HIV and Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined by :

1) Evidence of structural or functional kidney damage (abnormal urinalysis, imaging studies or histology) present for at least 3 months with or without a decrease in GFR ; or

2) Decreased kidney function (GFR<60ml/min per 1.73m²).

CKD is classified into 5 stages (Table 8) according to the GFR, which is calculated either using the Cockcroft-Gault equation or the MDRD (Modification of Diet in Renal Disease) equation (Table 9).

Stage	Description	GFR (ml/min per 1,73m²)
I	Kidney damage with normal or increased GFR	≥90
II	Kidney damage with mildly decreased GFR	60-89
III	Moderately decreased GFR	30-59
IV	Severely decreased GFR	15-29
V	Kidney failure	<15 (or dialysis)

Table 8 Stages of CKD(Levey et al. 2002)

Cockcroft-Gault equation	$\frac{(140 - \text{age}) \times \text{body weight (kg)}}{0.82 \times \text{serum creatinine}} \times (0.85 \text{ females})$
MDRD equation	$186 * [\text{s-Creat } (\mu\text{mol/l}) * 0.011312]^{-1.154} * [\text{age}]^{-0.203}$ * [0.742 if patient is female] * [1.212 if patient is black]

Table 9 GFR calculation (Levey et al. 2002)

1.5.1 *HIV-associated nephropathy*

HIV-associated nephropathy (HIVAN) is an entity that is now thought to be caused by a direct effect on renal cells by the Human Immunodeficiency Virus. HIVAN is the third leading cause of ESRD in African-Americans aged 20-64 in the United States (Ross et al. 2000), preceded only by diabetes and hypertension. Over 85% of cases in the USA occur amongst African-Americans (Monahan et al. 2001). In Africa, HIVAN is the most common presentation in HIV patients with CKD (Gerntholtz et al. 2006; Han et al. 2006).

HIVAN is associated with heavy proteinuria, absence of peripheral oedema, large echogenic kidneys and rapid progression to end stage renal disease (D'Agati et al. 1997). Szczech et al (2002) showed that 32% of HIV positive patients had proteinuria (> or =1+ on dipstick examination on at least 2 consecutive analyses); CD_4 counts $\leq$ 200 cells/µl, detectable HIV RNA level, increasing systolic blood pressure, decreasing serum albumin and increasing serum creatinine were all associated with the development of renal failure.

A series of 99 biopsies of HIV positive patients in Chris Hani Baragwanath Hospital, Johannesburg, South Africa during 2003 and 2004 categorized the classic HIVAN in 27% and HIVICK (HIV immune complex kidney disease) with sub-epithelial immune deposits in 21% (Gerntholtz et al. 2006).

Another study at the King Edward Hospital in Durban, South Africa, looked at the prevalence of CKD by screening for proteinuria in 615 HIV positive patients. Thirty-eight patients (6%) were found to have proteinuria and 32 out of 90 (36%) patients tested had microalbuminuria. Persistent microalbuminuria was found in only 7 patients. When biopsied, 6 of these 7 showed the presence of HIVAN. In total, 25 out of 30 (83.3%) renal biopsies showed HIVAN (Han et al. 2006).

Some work has gone into the various presentations of HIV nephropathy, but there is a paucity of information regarding predictors of outcome. A review of 16834 patients from 8 clinics in the United Kingdom between 1998 and 2004, identified HIVAN in 61 patients. Of these, 34 (56%) developed ESRD. HIVAN prevalence in black patients was 0.93%.There was no additional renal benefit in early initiation of HAART, viral suppression or CD_4 recovery in the cohort with HIVAN. The severity of CKD as quantified on biopsy was the strongest predictor of progression to ESRD. There was a statistically significant difference in the group with a higher index of chronic damage (ICD) score compared to those with a lower score. The median ICD score for 16 patients that developed ESRD was 84, as compared with a score of 31 for 12 patients who maintained stable renal function (Post et al. 2008).

1.5.2 *Potential causes of CKD in HIV positive patients*

There are a few associations with the various causes of CKD in HIV patients (see Table 10) such as hepatitis B and C with Membranous and Membranoproliferative GN.

GLOMERULAR PATTERN
HIVAN (HIV associated nephropathy)
HIVICK (HIV-immune complex kidney disease) Immune complex-mediated glomerulonephritis (GN) IgA nephritis Postinfectious GN Membranous GN Membranoproliferative GN Mesangial proliferative GN Fibrillary or immunotactoid GN Mixed inflammatory or sclerotic variant Lupus-like nephritis
Interstitial Nephritis
Thrombotic microangiopathies
Minimal change glomerulonephritis
Diabetic nephropathy
Hypertensive nephropathy

Table 10 Spectrum of glomerular disease with HIV (de Silva et al. 2007)

1.6 **HIV and electrolyte disorders**

HIV infection is associated with electrolyte and acid base imbalances. These can be attributable to HAART, other drugs, infections and other co-morbidities. Table 11 lists the electrolyte and acid-base abnormalities due to drugs used to treat HIV positive patients.

Sodium

Hyponatraemia is frequent in HIV infected individuals, with a reported incidence of 30-60% in hospitalized patients (Agarwal et al. 1989). Hyponatraemia is a marker of severe illness and prognostic of increased mortality in HIV infected patients (Tang et al. 1993). The common causes are volume depletion caused by diarrheoa and vomiting. Important causes also include the syndrome of inappropriate anti-diuretic hormone hypersecretion (SIADH) in hospitalized patients which is associated with pulmonary and intracranial diseases. This may direct one to identify opportunistic infections such as tuberculosis and Pneumocystis jiroveci pneumonia.

Potassium

Hypokalaemia is commonly found in patients with diarrhoea and vomiting. Drugs such as Amphotericin B and tenofovir can cause hypokalemia by causing renal tubular dysfunction. Drugs such as trimethoprim-sulfamethoxazoleand pentamidine can cause hyperkalaemia. Hyperkalaemia and hyponatraemia may be due to mineralocorticoid deficiency. Hyperkalaemia can also be due to acute or chronic renal failure.

Other

In a prospective cross sectional study of 1232 patients, the clinically relevant electrolyte abnormalities in HIV positive patients also included hyperuricaemia (41.3%), hypophosphataemia (17.2%) and low bicarbonate (13.6%) (Bagnis et al. 2007).

Hypernatraemia	Rifampicin, amphotericin B, foscarnet
Hyperkalaemia	Ketoconazole, trimethoprim
Hypokalaemia	Rifampicin, amphotericin B, didanosine, foscarnet, tenofovir
Hypomagnesemia	Amphotericin B, pentamidine
Hypocalcemia	Didanosine, pentamidine, foscarnet
Hypouricaemia	Rifampicin, tenofovir
Hyperuricaemia	Didanosine, pyrazanimide, ethambutol
Renal tubular acidosis	Amphotericin B, trimethoprim, rifampicin, foscarnet, cidofovir, Nucleoside- reverse transcriptase inhibitors (NRTI), Fanconi's syndrome with tenofovir
Normal Anion gap metabolic acidosis	Diarrheoa Adrenal insufficiency Renal tubular acidosis
Raised anion gap metabolic acidosis	Type A lactic acidosis : hypotension, hypovolaemia, sepsis, diabetic ketoacidosis Type B lactic acidosis : drug induced mitochondrial toxicity due to zidovudine, didanosine, lamivudine, stavudine, zalcitabine

Table 11 Electrolyte and acid base disturbances in HIV positive patients (Fabian and Naicker. 2009)

1.7 HIV and HAART nephrotoxicity

AKI is frequently caused by the toxic effects of antiretroviral therapy or nephrotoxic antimicrobial substances used in the treatment of opportunistic infections. Drugs associated with nephrotoxicity include aminoglycosides, amphotericin B, foscarnet, trimethoprim-sulfamethoxazole, tenofovir, indinavir and acyclovir.

Diabetes mellitus and the metabolic syndrome may be accelerated by lipid abnormalities associated with HAART. A study of 5578 patients during 1984-2003 revealed an incidence of hypertension of 7.3% among HIV positive individuals. The incidence increased significantly after 2 years of treatment (Seaberg et al. 2005). The common causes of CKD are diabetes and hypertension and the added burden by HAART compounds the numbers of patients with ESRD.

Nucleotide reverse transcriptase inhibitors

Tenofovir, adefovir and cidofovir have been associated with renal tubular damage (Verhelst et al. 2002). Tenofovir has been linked to Fanconi's syndrome consisting of a defect in the proximal tubule, causing loss of glucose, phosphate, calcium, uric acid, amino acids, bicarbonate and tubular proteins, which is usually reversible (Izzedine et al. 2005).

A recent meta-analysis reviewed the renal safety of Tenofovir Disoproxil Fumarate (TDF) in HIV infected patients. There were 17 studies (including 9 randomized controlled trials) that met the selection criteria and included a median sample size of 517 participants. There was a significantly greater loss of kidney function among the TDF recipients compared to the control subjects (mean difference in GFR, 3.92ml/min) as well as a greater risk of AKI (risk difference 0.7%). There was no evidence of increased risk of severe proteinuria, hypophosphataemia or fractures (Cooper et al. 2010).

Nucleoside Reverse Transcriptase Inhibitors

Renal toxicity is rare. Case reports with didanosine and lamivudine-stavudine have been associated with tubular dysfunction (Izzedine et al. 2005).

Non-nucleoside Reverse Transcriptase Inhibitors

Nevirapine, efavirenz and delaviridine have been demonstrated to be safe in controlled trials (Roling et al. 2006).

Protease Inhibitors

Indinavir has been most frequently associated with adverse renal effects including nephrolithiasis, crystalluria, dysuria, papillary necrosis and AKI (Daugas et al. 2005) Antiretroviral therapy given in combination with low dose ritonavir increases the toxicity of indinavir (Casado et al. 2000). Ritonavir has been associated with reversible renal failure (Bochet et al. 1998).

Saquinavir and nelfinavir have been demonstrated to be safe in controlled trials, but there has been a single case report of them causing renal calculi (Green et al. 1998).

Atazanavir, amprenavir, fosamprenavir and lopinavir have not been associated with renal toxicity.

Life expectancy is increasing with the advent of HAART and thus the spectrum of renal disease in HIV patients will include an increased prevalence of diabetes mellitus, hypertension and other chronic diseases (Roling et al. 2006).

1.8 Hypothesis

Outcomes of AKI are similar in HIV positive and HIV negative patients.

1.9 Objectives

1) To describe the presentation of renal failure in HIV positive patients.
2) To determine the clinical and laboratory features of AKI in HIV positive patients.
3) To compare AKI between HIV positive and HIV negative patients with regards to clinical features and outcomes.

CHAPTER 2 PATIENTS AND METHODS

2.1 Study Design

A single-centre retrospective review of patients presenting to the acute renal service of the Division of Nephrology at Charlotte Maxeke Johannesburg Academic Hospital, a referral tertiary hospital draining the greater Johannesburg area,was conducted during the period 1st October2005 until 31st October 2006.Patients were seen daily by the registrar and Nephrology consultant on call for the week in the acute renal unit. The study aimed at reviewing data of HIV positive patients with renal failure. Those presenting with AKI were further reviewed to compare data with a randomly chosen cohort of HIV negative patients. Young HIV negative patients presenting with renal failure were chosen to attempt to age match with the HIV negative group and these were chosen as monthly consecutive referrals after the HIV positive patients.

The inclusion criteria included patients who were

- over the age of 18 years
- presented to the CMJAH between 1st October 2005 and 31st October 2006
- consulted by the adult renal unit

The identities of all patients were and will be kept confidential. The first two letters of the name and surname of the patients were used as the codename for the patients. After collecting the information on the data collection sheet, all data was transformed onto the spreadsheets (see Appendix 7 and 8).

Demographic data, laboratory results and other information was abstracted from the weekly records kept in the "acute renal'' database. Renal summaries and the hospital files were reviewed where available.

Ethics approval was granted unconditionally by the University of the Witwatersrand Ethics committee. (Clearance certificate M070427)

Data that was collected included:

- age
- sex
- race
- ward
- diagnosis (AKI, AOCRF, CKD)
- aetiology of renal failure (sepsis, haemodynamic instability, toxins, urological obstruction, miscellaneous)
- co-morbidities
- hypertension
- diabetes
- tuberculosis
- serum electrolytes (sodium, potassium, chloride, bicarbonate)
- serum calcium, magnesium, phosphate
- serum urea & creatinine (admission, inpatient, discharge)
- days of recovery (from admission to lowest serum creatinine)
- leucocytes (in blood)
- haemoglobin
- platelets
- albumin
- CD_4
- hepatitis
- urine protein-creatinine ratio
- urine microscopy and culture
- blood culture
- dialysis
- kidney size
- outcome

- Hypertension was defined using the South African Hypertension Society guidelines

  i.e. SBP>140 and/or DBP >90, or known hypertensive patient on medication.

- Diabetes mellitus was diagnosed by the attending medical doctors. Local SEMDSA guidelines were used.
- Tuberculosis was diagnosed by the identification of acid fast bacilli in sputum, bone marrow,TB bactec or by the attending medical doctor's judgment of the patient's chestX-ray.
- Serum electrolytes including sodium, potassium, chloride and bicarbonate together with blood urea and serum creatinine were collected on admission. The lowest serum creatinine and the serum creatinine on discharge were collected as well. The days of recovery were calculated by reviewing the serial creatinine levels and the lowest levels achieved.
- Urine dipstix results were obtained where possible.
- Urine microscopy, culture & sensitivity was obtained.

  Urine leucocyte number and erythrocyte number were obtained.
- Proteinuria was obtained from a spot urine PCR and/or dipstix proteinuria.
- The organisms cultured from the blood were documented.
- Dialysis was initiated according to standard indications (see Table 5). The mode of dialysis used was haemodialysis.
- Kidney size was documented using ultrasonography by the radiology unit.
- Some patients were treated conservatively, without dialysis. These included foreign nationals with CKD (after counseling regarding private funding) and patients deemed to have a poor prognosis.
- Outcome was measured as either recovery or death.

Patients were stratified (opinion-based) into 3 groups, namely AKI, AOCRF and CKD. The files were reviewed by a senior nephrologist (Dr S Wadee) and myself. The reviewed data that helped stratify the groups included:

- Past medical history of CKD
- Serum creatinine

  Recovery of serum creatinine within 3 months is defined as AKI.As most consultations were in-hospital, data was not available for follow-up. Hence, the improvement of renal function was reviewed by the difference in the admission creatinine and the lowest creatinine achieved or independence from dialysis if previously dialysis requiring.

- Haemoglobin

  Anaemia cannot be reliably used to diagnose CKD; moreover in HIV patients a low haemoglobin could be attributable to bone marrow failure, infiltrations and infections, haemorrhage, haemolysis amongst other causes.

- Serum calcium and phosphate

  While CKD is associated with a hypocalcaemia and hyperphosphataemia, these electrolyte changes are also present in later stages of AKI or with specific causes of AKI such as rhabdomyolysis.

- Renal sonar

  Small kidneys are associated with CKD. However, there are a few conditions that cause enlarged kidneys such as diabetes mellitus, multiple myeloma, polycystic kidney disease, renal cell carcinoma, infiltrative conditions such as amyloidosis and HIV associated nephropathy. Therefore enlarged kidneys could be present in any HIV positive patient with acute or chronic renal failure.

AKI was defined as an improvement in admission serum creatinine >50% (Kellum 2008). This group was further subdivided using the RIFLE criteria into 'Risk', 'Injury' and 'Failure'. Using a serum creatinine of < 97µmol/L as normal (as referenced by the National Health Laboratory Service at the CMJAH), the three groups were categorized as below:

RIFLE classification		**serum creatinine (µmol/L)**
Risk	serum creatinine > 1,5	< 194
Injury	serum creatinine > 2	195 – 291
Failure	serum creatinine > 3	> 291

Those patients that recovered renal function partially (improvement in serum creatinine less than 50%) with evidence of underlying CKD were categorized as AOCRF.

The definition of CKD applies to those patients whose serum creatinine does not improve after 3 months or with persistent proteinuria. Data that was collected included in-hospital consultations, thus strict criteria to the definition could not be observed as follow-up data for up to 3 months was not available for most patients, who were lost to follow up. Those patients with small kidneys (<9cm) were classified as CKD.

2.2 **Statistical methods**

Statistical analysis was done using a commercially available package, namely STATISTICA (version 9).

Descriptive statistics was done using measures of location (mean, median ,mode) and measures of spread (standard deviation, range) for continuous variables. Frequency distribution tables were used for categorical variables. Pie and bar charts were used for categorical variables.

Bivariate analysis for pairs of categorical variables was done using Pearson's Chi Square (Fisher's exact when appropriate). The Student's t-test was used for pairs of normally distributed continuous variables.

The Shapiro Wilk test for normality of data was used for assessment of skewness and kurtosis. (see Appendix 5)

Statistical significance was ascertained at the 5% level (a p-value of less than 0.05 to imply significance).

CHAPTER 3 RESULTS

3.1 HIV positive patients presenting with renal failure

3.1.1 Demographic and clinical data

In the period reviewed, 684 patients presented with renal failure to the Adult Renal Unit at the Charlotte Maxeke Johannesburg Academic Hospital. Of these, 101 patients were HIV positive (14.8%). The patients were predominantly black (99 patients) and there were 56 males. The average age was 38years ±9.89 (range 21 – 61years).

Presentation

Most HIV positive patients presented with AKI (57 patients), followed by CKD (23 patients) and lastly AOCRF (21 patients) (Figure 4).

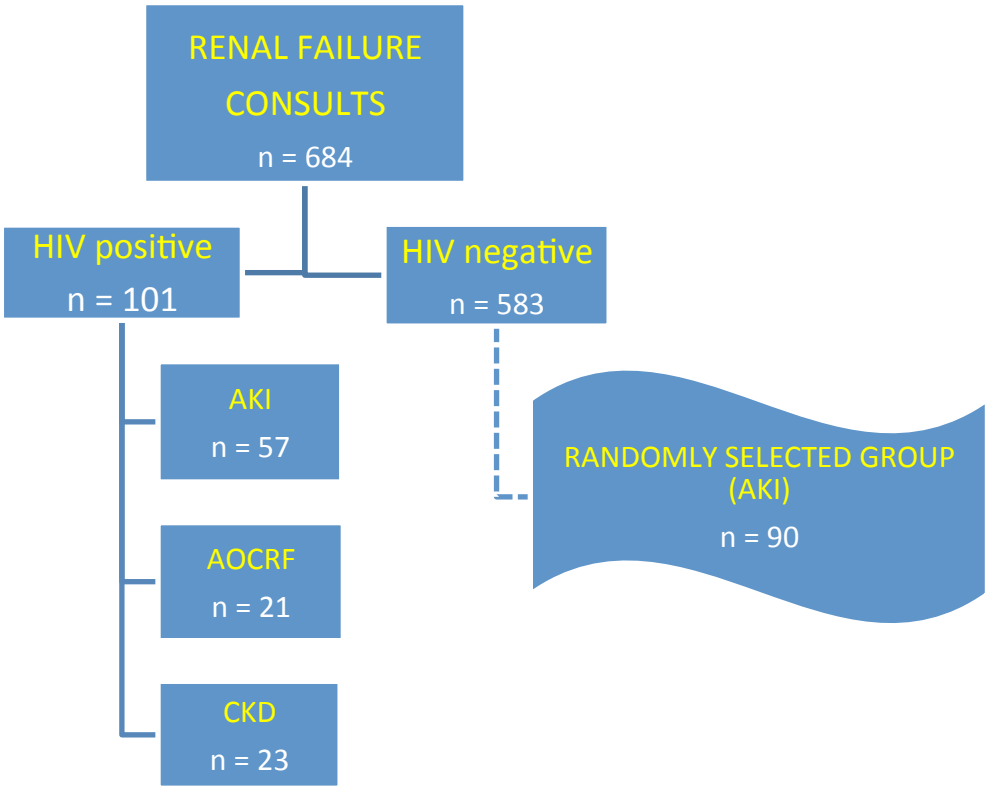

Figure 4 Flow diagram (patient presentation)

Aetiology of Renal Failure

The patients were further classified according to the aetiology of the renal failure (see Table 12).

- sepsis
- haemodynamic instability
- toxin
- urological obstruction
- miscellaneous

Those in the sepsis groups were classified by file review including blood and urine culture and sensitivity. Those with haemodynamic instability included pre-renal patients, predominantly those dehydrated secondary to gastrointestinal losses but also conditions such as cardiac failure and haemorrhage.

Toxins included contrast agents used for diagnostic scans, 'Muti' (traditional medicines), drugs such as aminoglycosides and amphotericin B.

Urological obstruction included those patients presenting with urinary retention secondary to masses (infectious or neoplastic), prostatic pathology and drugs.

Those presentations not included in the above groups were placed into the miscellaneous group.

	AKI	AOCRF	CKD
N	**57**	**21**	**23**
Sepsis	34 (60%)	15 (71%)	11 (48%)
Haemodynamic	11(19%)	2 (10%)	0
Toxin	5 (9%)	0	3 (13%)
Obstruction	4 (7%)	0	0
Miscellaneous	8 (14%)	2 (10%)	5 (22%)

Table 12 Aetiology of renal failure (HIV positive patients)

Location of patients

The majority of the consultations were from the medical ward (81 patients), followed by the Medical Intensive Care Unit , Obstetrics and Gynaecology wards and the smallest numbers coming from the surgical wards (Table 13).

WARD	HIV positive
Medical	81
ICU	10
Surgical	4
Obstetrics & Gynaecology	6

Table 13 Ward admissions (HIV positive patients)

Co-morbid conditions

Chronic diseases

Hypertension was present in 11 patients (Table 14) and diabetes mellitus in 6 patients.

	ALL	AKI	AOCRF	CKD
SBP (mmHg)	123	108	125	157
DBP (mmHg)	76	69	75	93

Table 14 Blood pressure in HIV positive patients

Infectious Diseases

Tuberculosis was identified in 22 patients.

Hepatitis B co-infection was present in 5 patients and Hepatitis C in 2 patients.

The predominant organism cultured from the blood was S.pneumonia (Table 15).

		ALL	AKI	AOCRF	CKD
Blood Culture	S.pneumonia	5	3	1	1
	S. aureus	2	0	0	2
	MRSA	4	3	1	0
	E.Coli	3	2	1	0
	S.typhi	2	2	0	0
Urine	E.Coli	9	4	3	2
	K. pneumonia	4	3	1	0

Table 15 Culture results in HIVpositive patients

Methicillin resistant Staphylococcus aureus (MRSA) was cultured in 4 patients. E.coli and K.pneumonia were the most common organisms cultured in the urine.

Renal replacement therapy

Haemodialysis was initiated in 43 individuals (Table 16).

	N	AKI	AOCRF	CKD
Dialysed	43	22	8	13

Table 16 Haemodialysis in HIV positive patients

*3.1.2 **Laboratory data***

Proteinuria

The average level of protein in the urine was 0.61mg/mmol. As the categories of renal failure progressed from acute to chronic, so did the amount of proteinuria, as measured by the urine PCR (see Figure 5).

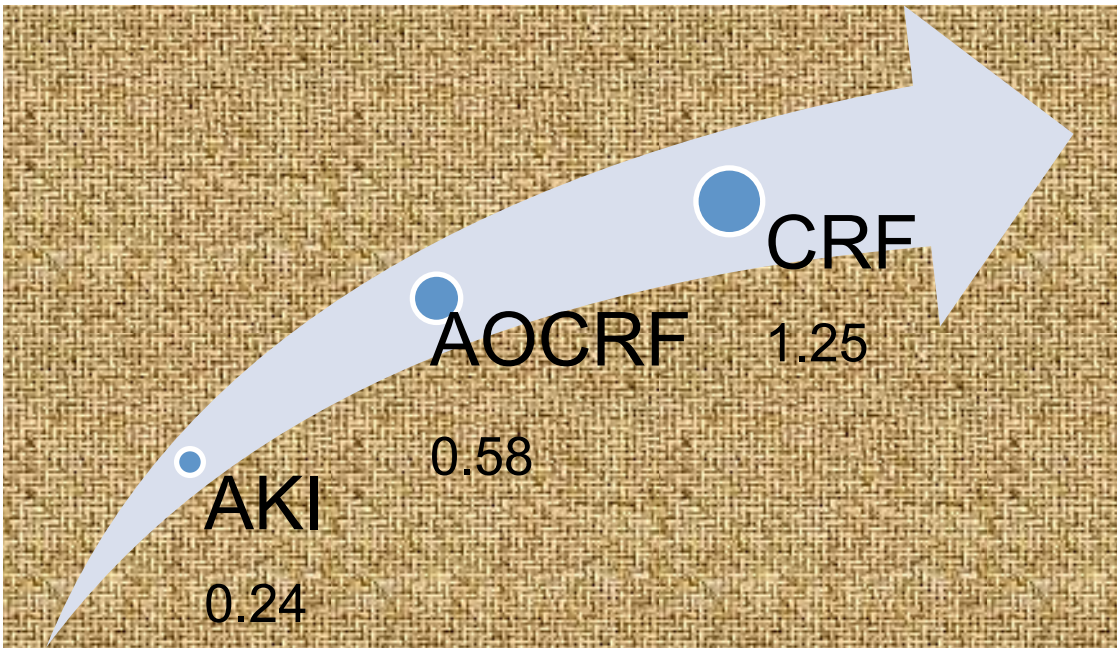

Figure 5 Urine protein-creatinine ratio

CD4 count

The mean CD4 count was 135cells/µl. More than 50% of the patients had a CD4count below 100cells/µl. Of interest was that the lowest CD4 counts were found in the AOCRF group (see Figure 6).

Figure 6 Mean CD4 count (cells/µl) in the 3 categories of renal failure

	N	ALL (mean)	AKI	AKI (mean)	AOCRF	AOCRF (mean)	CKD	CKD (mean)
CD4	88	135.3	49	146.1	18	74.8	20	170.2
CD4<200	63		36		16		11	
CD4<100	**52**		**33**		**9**		**10**	
CD4<50	37		21		10		6	

Table 17 CD4 count (cells/µl) in HIV positive patients

3.2 HIV positive patients presenting with Acute Kidney Injury

There were 57 patients who presented with AKI. Amongst this group 7 patients were not included in the comparison with HIV negative patients as their data was not sufficient.

The patients with AKI were divided using the 'RIFLE' classification into 3 groups; Risk, Injury and Failure (see Table 18).

RIFLE classification	Serum creatinine (mg/dl)	Number of patients with AKI (%)
Risk	serum creatinine > 1,5	4 (8)
Injury	serum creatinine > 2	10 (20)
Failure	serum creatinine > 3	36 (72)

Table 18 RIFLE classification (HIV positive group)

3.3 HIV negative patients presenting with Acute Kidney Injury

In the HIV negative group, 90 randomly selected patients were evaluated. These HIV negative patients were age and gender matched as far as possible from the acute renal unit database. The group was also divided using the RIFLE criteria into 3 groups; Risk, Injury and Failure.

RIFLE classification	Serum creatinine (mg/dl)	Number of patients with AKI (%)
Risk	serum creatinine > 1,5	26 (29)
Injury	serum creatinine > 2	24 (27)
Failure	serum creatinine > 3	40 (44)

Table 19 RIFLE classification (HIV negative group)

3.4 Comparison between HIV positive and HIV negative patients with AKI

Acute kidney injury was reviewed by comparing the demographic, clinical and laboratory parameters between the HIV positive and HIV negative groups as well as their outcomes. There were 50 HIV positive patients and 90 HIV negative patients selected as previously discussed and they were further subdivided using the RIFLE classification (Table 20).

RIFLE classification	HIV positive (%)	HIV negative (%)
Risk	4 (8)	26 (29)
Injury	10 (20)	24 (27)
Failure	36 (72)	40 (44)

Table 20 Comparison in presentation of AKI

Demographic data included age, sex and race.

Clinical data included aetiology of AKI, wards, dialysis, days to recovery, co-morbid conditions such as chronic diseases (hypertension and diabetes mellitus) and infectious diseases (tuberculosis and hepatitis) and renal sonar size

Laboratory data included electrolytes, urea and creatinine, haemoglobin, albumin, hepatitis B and C, urine and blood cultures.

There were two outcomes assessed; survival and death.

3.4.1 *Demographic and clinical data*

Age

HIV positive : The mean age was 37.42 years ± 10.45 (range 21-67 years)

HIV negative : The mean age was 45.20 years ± 16.97 (range 18-84 years)

	HIV positive	HIV negative
Survived	37.36 years	49.23 years
Died	37.46 years	41.49 years

Table 21 Outcome (age)

Gender

HIV positive : There were 22 (44%) females and 28 (56%) males.

HIV negative : There were 35 (39%) females and 55 (61%) males.

There were more females in the HIV positive group as compared to the HIV negative group

(44% vs 39%). (p=0.564)

Males

	HIV positive (%)	HIV negative (%)
Recovered	28 (56)	48 (53)
Died	22 (44)	42 (47)

Table 22 Outcome of males

Females

	HIV positive (%)	HIV negative (%)
Recovered	22 (44)	42 (47)
Died	28 (56)	48 (53)

Table 23 Outcome of females

Race

	HIV positive (%)	HIV negative (%)
Black	49 (98)	67 (74)
White	1	15
Indian	-	6
Coloured	-	2

Table 24 Race (AKI)

Majority of the HIV positive patients were black (98%) and this was statistically significant when compared to the HIV negative group ($p<0.0004$).

In the HIV negative group there was a more varied racial grouping.

Location

	HIV positive (%)	HIV negative (%)
Medical	37 (74)	43 (48)
Surgical	4 (8)	22 (24)
ICU	6 (12)	15 (17)
Obstetrics/Gynaecology	3 (6)	10 (11)

Table 25 Location of patients referred with AKI

In the HIV positive group the majority of the patients were from the medical wards (74%) as compared to the HIV negative group (48%) (Table 25) and this was statistically significant ($p<0.0022$). The HIV negative patients were more likely to come from the non-medical wards as compared to the HIV positive patients.

		HIV positive (%)	HIV negative (%)
Survived	Medical	23 (46)	25 (27.8)
	Surgical	3 (6)	11 (12.2)
	ICU	-	4 (4.4)
	Obstetrics/Gynaecology	2 (4)	8 (8.8)
Dead	Medical	14 (28)	18 (20)
	Surgical	1(2)	11 (12.2)
	ICU	6 (12)	11 (12.2)
	Obstetrics/Gynaecology	1 (2)	2 (2.2)

Table 26 Outcome of AKI according to referring departments

Aetiology of AKI

	HIV positive (%)	HIV negative (%)
Sepsis	31 (62)	39 (43)
Haemodynamic	10 (20)	15 (17)
Toxin	5 (10)	6 (6)
Urological obstruction	4 (8)	7 (8)
Miscellaneous	5(10)	21 (23)

Table 27 Aetiology of AKI

Sepsis was the predominant cause of AKI in both groups but was more common in the HIV positive group (Table 27). Figure 7 is a comparison of the different aetiologies of AKI between the HIV positive and the HIV negative groups.

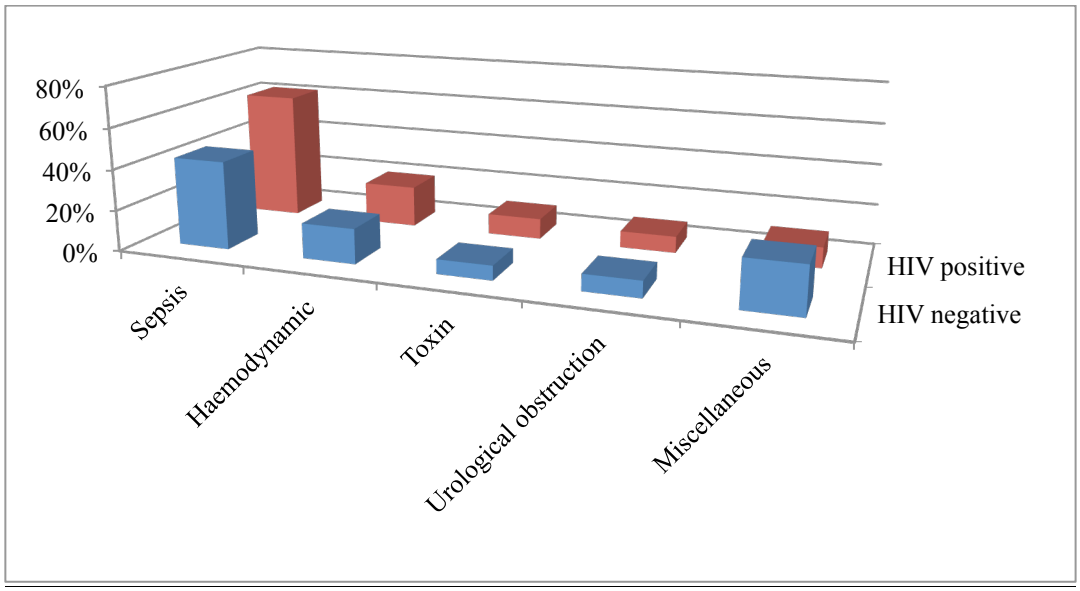

Figure 7 Comparison of aetiology of AKI in HIV positive and HIV negative patients

Renal replacement therapy (Haemodialysis)

In the HIV positive group 18/50 (36%) patients were dialyzed as compared to the HIV negative group where 35/90 (39%) were dialyzed.

	HIV positive (%)	HIV negative (%)
Survived	7 (14)	20 (22)
Dead	11 (22)	15 (17)

Table 28 Outcome of patients with AKI that were dialysed

Fluid Therapy

For those patients that were not dialysed and treated with fluid therapy and antibiotics where indicated, 42% of HIV positive patients recovered as compared to 31% of HIV negative patients.

	HIV positive (%)	HIV negative (%)
Survived	21 (42)	28 (31)
Dead	11 (22)	27 (30)

Table 29 Outcome of patients with AKI treated with fluid therapy

Those patients presenting with AKI that recovered with fluid therapy (i.e. were not dialyzed) were evaluated in their days to recovery. HIV positive patients recovered in 9.79 days ± 6.16 (3-28days) and HIV negative patients recovered in 10.06 days ± 5.76 (2-24days).

Chronic diseases

There was only 1 patient with diabetes mellitus and 2 patients with hypertension in the HIV positive group, compared to 13 patients with diabetes mellitus and 19 patients with hypertension in the HIV negative group.

Infectious Diseases

In the HIV positive group, 13 patients were diagnosed with tuberculosis as compared to only 2 in the HIV negative group. Hepatitis B was present in 2 of the HIV positive patients.

Renal sonar size

	HIV positive	HIV negative
Right kidney (cm)	12.11	10.96
Left kidney (cm)	12.21	11.24

Table 30 Renal size on ultrasound

HIV positive patients had larger renal sonar sizes than HIV negative patients ($p < 0.0001$, t-test).

3.4.2 *Laboratory and outcome data*

*Characteristics		HIV positive	HIV negative	p
Number		50	90	
Electrolytes				
Na (mmol/l)		132	139	<0.0001
K (mmol/l)		4.9	4.5	0.0426
Cl^- (mmol/l)		98	103	0.0121
CO2 (mmol/l)		14.7	19.4	0.0002
Urea (mmol/l)	(admission)	34.5	23.3	0.0013
Creatinine (µmol/l)	(admission)	619	455	0.07
Calcium (mmol/l)		2.28	2.33	ns
Magnesium (mmol/l)		1.09	0.93	ns
Phosphate (mmol/l)		2.49	1.78	0.0004
Haemoglobin (g/dl)		10.02	10.84	ns
Albumin (g/dl)		27.17	28.58	ns
Hepatitis B		2		ns
Urine PCR		0.26	0.28	ns
Survived (%)		56	52	0.694
Died (%)		44	47	0.7173

Table 31 Laboratory and outcome data (AKI)

Electrolytes

HIV positive patients presented more hyponatraemic (p<0.0001, t-test), hyperkalaemic (p=0.0426, t-test) and hypochloraemic (p=0.0121, t-test) compared to the HIV negative patients and this was statistically significant (see Table 33). HIV positive patients were also more acidotic (p=0.0002, t-test). Serum calcium and magnesium levels were similar, however HIV positive patients were more hyperphosphataemic compared to HIV negative patients, which was statistically significant (p=0.0004, t-test).

Urea and Creatinine

HIV positive patients had a higher baseline mean serum creatinine on admission than the HIV negative patients.

	HIV positive	HIV negative
Creatinine (µmol/l) (admission)	619 ± 407	455 ± 561
Creatinine (µmol/l) (lowest)	202 ± 143	170 ± 103

Table 32 Serum creatinine levels

Excluding those patients that were dialysed, the following observation was made; HIV positive patients recovered to a lower serum creatinine than HIV negative patients with supportive care over a shorter period.

	HIV positive	HIV negative
Creatinine (µmol/l) (lowest)	157 ± 72	184 ± 118

Table 33 Serum creatinine improvement with fluid therapy

Haemoglobin

Haemoglobin levels were similar and not statistically significant when comparing HIV positive and HIV negative patients.

	HIV positive	HIV negative
Haemoglobin (g/dl)	10.02 ± 3.01	10.84 ± 3.09

Table 34 Haemoglobin levels in AKI patients

Albumin

Albumin levels were similar and not statistically significant between HIV positive and HIV negative patients.

	HIV positive	HIV negative
Albumin (g/dl)	27.17 ± 8.37	28.58 ± 8.56

Table 35 Serum albumin levels in patients with AKI

Urine PCR

	HIV positive	HIV negative
Urine PCR (g/mmol)	0.26	0.28

Table 36 Urine PCR (AKI)

Urine PCR did not differ between the two groups of patients as there was no statistical significance.

	HIV positive	HIV negative
Survived	0.263	0.316
Dead	0.259	0.234

Table 37 Outcome (urine PCR)

Urine PCR was not a reliable predictor of outcome as this test was only done in 22 of the 90 HIV negative patients.

CHAPTER 4 DISCUSSION

4.1 Presentation of renal failure in HIV positive patients

HIV positive patients presented more commonly with AKI (57 of the 101 patients) than AOCRF and CKD. The mean age of the HIV positive patients presenting with renal failure was 38 ± 9.89 years. Previous studies have shown similar mean ages of HIV positive patients with renal failure ranging from 35 years to 46.7 years (Rao et al. 1995; Peraldi et al. 1999; Franceschini et al. 2005; Wyatt et al. 2006). Males represented the majority of patients in previous studies (see Appendix 5). There were almost equal numbers of males and females reviewed with AKI in this study (56% males).

Patients presenting in our setting with renal failure who were HIV positive were more likely to be black. There were 98 out of 101 HIV positive patients with renal failure that were black. The only similar study showing 99% of the patients presenting with acute kidney injury to be black was the study by Rao et al. The studies by Wyatt, Ibrahim and Franceschini each showed the percentage of black patients with acute kidney injury to be 54.5 %, 55% and 61 % respectively. The racial predominance is different to other countries which might be due to epidemiological factors and the spread of HIV. In the literature, HIVAN is predominantly found in the black race. The majority race in South Africa is black and the predominance of black patients that are HIV positive presenting with renal failure is evident.

The majority of consultations for patients with renal failure that were HIV positive came from the medical wards (81%). When the aetiology of renal failure is reviewed, the commonest cause of renal failure was sepsis (60%) followed by haemodynamic instability. Urological obstruction was the least common cause of renal failure (4%). Sepsis was also the predominant aetiology of renal failure in other studies. Rao et al showed that sepsis was the most common aetiology (52%) in hospitalized patients. Sepsis was the most frequent cause of AKI in the retrospective review by

Peraldi et al, accounting for 75% of cases. Other studies (see Appendix 5) showed that sepsis was less common, however these included ambulatory and not hospitalized patients (Franceschini et al. 2005; Ibrahim et al. 2010).

AKI patients presented in a hypotensive state more frequently compared to those with AOCRF and CKD individuals, with a mean BP of 108/69. This was due to AKI representing 85% of cases of haemodynamic instability, including hypovolaemia.

Hyponatraemia was common amongst all three groups, but most severe in the AKI patients. The study by Agarwal et al reported the incidence of hyponatraemia in HIV infected patients as 30-60% and Tang et al showed that it was a marker of severe illness and prognostic of increased mortality in HIV positive patients. The common causes of hyponatraemia include diarrheoa and vomiting but important causes including SIADH must be excluded.

HIV positive CKD patients presented with more severe hyperkalaemia and acidosis. This could be secondary to the renal failure or concomitant drugs such as trimethoprim-sulfamethoxazole. Mineralocorticoid deficiency could also account for the hyperkalaemia and also hyponatraemia. The mean haemoglobin was 8.44mg/dl which was expectedly lower than the AKI group (9.98 mg/dl). CKD patients also were appropriately more hypocalcaemic and hyperphosphataemic than the other patients in keeping with chronicity.

The mean CD_4 count of all the groups was 135 cells/µl. There were 63% of patients with AKI that had CD_4 count <200cells/µl. In the study by Franceschini et al only 29% had CD_4<200cells/µl. The mean CD_4 count in the AOCRF patients was almost half (75cells/µl) that of AKI patients (146 cells/µl) and CKD (170cells/µl) patients. This could possibly be due to the fact that these patients had underlying CKD and with compromised renal function and the lower CD_4 count made these patients more susceptible to an acute illness warranting admission.

S.pneumonia, Methicillin-resistant Staphylococcus aureus, E.coli and Salmonella infections were identified more commonly in the AKI group when compared to the CKD group, however in the chronic group Staphylococcus aureus was more common.

Urine leucocytes were present in more than half of all the patients.

	Urine leucocytes
AKI	32/57 (65%)
AOCRF	13/21 (62%)
CKD	13/23 (57%)

Table 38 Urine leucocytes (HIV positive group)

E.coli was cultured in the urine in all three groups. K. pneumonia was not present in the chronic group.

Urine PCR on admission in the AKI, AOCRF, CKD group was 0.24, 0.58 and 1.25 respectively. There was nephrotic range proteinuria in the AOCRF group and significant proteinuria in the CKD group (see Figure 8).

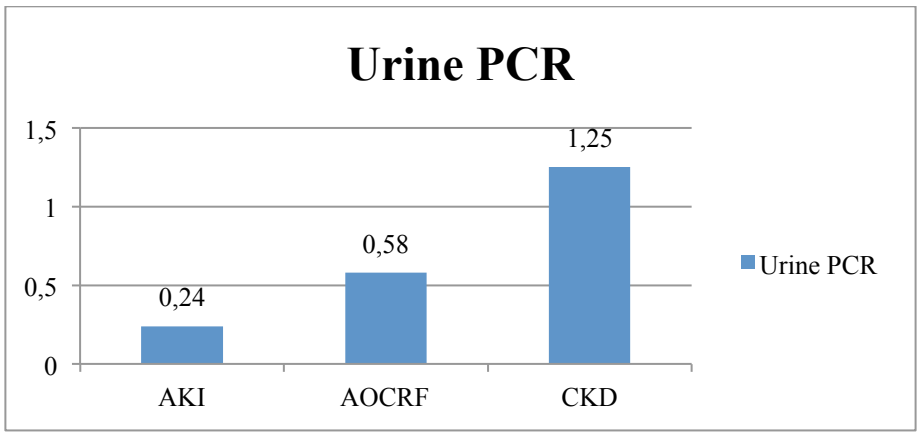

Figure 8 Urine PCR (HIV positive group)

4.2 HIV and Acute Kidney Injury

HIV positive patients with AKI presented with more severe renal failure than HIV negative patients. Using the RIFLE classification, 72% of HIV positive patients presented in the most severe clinical category ('Failure') as compared to 44% of HIV negative patients. Conversely, 29 % of HIV negative patients presented in the least severe clinical category ("Risk') as compared to only 8% of HIV positive patients.

The majority of patients in the HIV positive group were black (98%) as compared to the HIV negative group (74%) and this was statistically significant ($p = 0.0004$). There was a more varied racial distribution in the HIV negative group.

HIV positive patients presented more commonly to the medical wards with AKI when compared to the HIV negative patients (74% vs 48%).This was statistically significant ($p=0.0022$). There were 3 times more HIV negative patients admitted in the surgical wards than HIV positive patients (24% vs 8%).

Sepsis was the predominant cause of AKI in the HIV positive group (62%) and was also the more common aetiology when compared to the HIV negative group (43%). HIV positive patients presented with toxin ingestion slightly more commonly than HIV negative patients (10% vs 6%) and similar presentations with urinary obstruction (8%).

Chronic diseases such as hypertension and diabetes were more commonly associated with AKI in the HIV negative group as compared to the HIV positive group. There were 19 patients diagnosed with hypertension and 13 patients with diabetes in the HIV negative group and 2 patients with hypertension and 1 patient with diabetes in the HIV positive group.

Infectious diseases were more commonly present in the HIV positive group. Tuberculosis was present in 13 of the 50 patients with AKI in the HIV positive group as compared to 2 patients in the HIV negative group. Hepatitis B was present in 2 HIV positive patients with AKI.

Anaemia was more severe in the HIV positive patients with AKI (10.02 vs 10.84g/dl) and HIV positive patients presented more hypoalbuminaemic than HIV negative patients (27.17 vs 28.58g/dl).

In keeping with the literature (Agarwal et al. 1989), the HIV positive patients presented more hyponatraemic than the HIV negative patients. The HIV positive patients also presented more hyperkalaemic, hypochloraemic and more acidotic than HIV negative patients with AKI. HIV positive patients with AKI also presented with higher magnesium and phosphate levels than the HIV negative patients.

HIV positive patients with AKI had larger renal sizes using ultrasonography than HIV negative patients (Right 12.11cm vs 10.96cm ; Left 12.21 vs 11.24cm).

4.3 **Outcome of renal failure in HIV positive patients**

The two outcomes observed were survival and death. Overall 33 of the 101 HIV positive patients died, 22 in the AKI group, 6 in the AOCRF group and 5 in the CKD group.

Focusing on the AKI group the following observations were made.

There were more females in the HIV positive group as compared to the HIV negative group (44% vs 39%), but gender did not have an impact on outcome.

All 6 HIV positive patients with AKI admitted to ICU died.

An equal percentage of HIV positive patients that were dialyzed and those that were treated with fluid therapy died (22%). More HIV positive patients recovered with fluid therapy compared to HIV negative patients (42% vs 31%), suggesting that volume depletion was frequent in this group. Those HIV positive that did recover with fluid therapy, did so sooner than HIV negative patients (9.79 days vs 10.06 days).

Urine PCR was measured in 27/50 HIV positive patients with AKI and there was not much difference in the values when recovery and death were compared. The HIV negative patients that recovered had more proteinuria than those that died (0.316 vs 0.234).

	HIV positive (n = 27)	HIV negative (n = 22)
Survived	0.263	0.316
Dead	0.259	0.234

Table 39 Outcome (urine PCR)

Using urine PCR as an indicator for triaging patients according to chronicity of kidney failure had its limitations as this investigation was only done in 22 of the 90 HIV negative patients reviewed.

	HIV positive (%)	HIV negative (%)	p
Survived	56	52	0.694
Died	44	47	0.7173

Table 40 Outcome (AKI)

When reviewing the International literature (see Appendix 5), it is evident that AKI in HIV positive patients carries a high mortality; however there was no statistically significant difference in outcome between the two groups, hence it can be stated that the outcomes of HIV positive and HIV negative patients presenting with AKI were similar.

4.4 Conclusion

Outcomes of AKI are similar in HIV positive and HIV negative patients with adequate supportive care.

HIV positive patients should be treated acutely just as HIV negative patients. Dialysis should be offered when indicated and aggressive fluid resuscitation, antibiotics as well as other supportive care should be emphasized as it is likely that a higher percentage of patients will recover.

4.5 **Limitations**

This was a retrospective review, thus the completeness of data collection was not fully satisfactory. A prospective study would have created more validity.

Acute kidney injury has many different definitions. The 'RIFLE' classification is universally used, however different laboratories use different serum creatinine levels and many centers do not accurately measure urine output. We were limited as the baseline serum creatinine used was the admission creatinine and most of the patients were managed as inpatients and did not return to follow up as outpatients after discharge. Thus the definition of AKI as having normal renal function at 90 days could not be fulfilled. Thus the term 'probable AKI' would be more appropriate.

Some investigations (e.g. urine PCR) were not equally conducted in all patients in the HIV positive and HIV negative groups.

The patients in the two groups were not ideally matched, hence direct comparison would have been better in a prospective study.

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Appendix 1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Vachiat

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070427**
PROJECT	Outcome of HIV Patients presenting with Renal Failure at Johannesburg Hospital
INVESTIGATORS	Dr A Vachiat
DEPARTMENT	Nephrology
DATE CONSIDERED	07.05.04
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.08.24 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Wadee S Dr

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2

DATA COLLECTION SHEET

Date of admission: _____ HIV Yes☐ No☐
Name : _____
Hospital No. : _____
Age: ____
Sex: **M**☐ **F**☐

Race: **B** ☐ **W**☐ **C**☐ **I**☐

Renal Failure: AKI ____
ACUTE ON CHRONIC ____
CKD ____

Co-Morbidities:
_____

Dialysed: **Yes**☐ **No**☐

	(admission)	(lowest)	(discharge)
Urea	____	____	_____
Creatinine	____	____	_____

Admission results
Hb ____
WCC ____
Platelets ____
Na ____
K ____
Cl ____
CO_2 ____
Ca ____
Mg ____
PO4 ____
U.A ____
Urine PCR ____
Albumin ____
CD_4 ____
Hepatitis studies ____
Renal size (sonar) ____ ____
Other _____

Not qualifying for dialysis programme _____

Outcome: Renal Recovery/Discharge _____
RIP _____

Summary of HIV positive patients Appendix 3

	N	ALL (mean)	AKI	AKI (mean)	AOCRF	AOCRF (mean)	CKD	CKD (mean)
N	101		57		21		23	
Aetiology Sepsis	60		34		15		11	
Haemodynamic	13		11		2		0	
Toxin	8		5		0		3	
Urological obstruction	4		4		0		0	
Miscellaneous	15		8		2		5	
DIALYSED	43		22		8		13	
SBP (mmHg)	77	123	42	108	18	125	17	157
DBP (mmHg)	77	76	42	69	18	75	17	93
Na (mmol/l)	101	133	57	132.42	21	134.43	23	133.09
K (mmol/l)	101	4.96	57	4.92	21	4.83	23	5.18
Cl (mmol/l)	101	99.12	57	98.23	21	102.10	23	98.61
CO_2 (mmol/l)	101	14.02	57	14.97	21	14.29	23	11.44
Urea (mmol/l) (admission)	101	38.60	57	35.42	21	32.76	23	51.83
Serum creatinine (µmol/l) (admission)	101	827.50	57	633.57	21	677.95	23	1444.74
Urea (mmol/l) (lowest)	77	18.40	47	12.94	15	27.30	15	23.44
Serum creatinine (µmol/l) (lowest)	77	370.23	47	209.96	15	419.27	15	823.4
Duration of renal recovery (days)	76	14.96	47	17.17	15	10.93	14	11.86
Urea (mmol/l) (discharge)	92	56.87	50	61.52	21	52.76	21	49.91
Serum creatinine (µmol/l) (discharge)	57	653.61	26	418.31	15	619.20	16	1068.25
White cell count	101	11.12	57	10.72	21	10.76	23	12.44
Haemoglobin (g/dl)	101	9.35	57	9.98	21	8.66	23	8.44
Platelets ($x10^9$/l)	100	269.09	57	262.77	20	288.90	23	267.52
Albumin (g/dl)	95	26.76	53	26.60	19	27.26	23	26.70
Hepatitis B	5		2		0		3	
Hepatitis C	2		1		1		0	
CD_4 count (cells/µl)	88	135.31	49	146.08	18	74.78	20	170.15
CD_4 <200	63		36		16		11	
CD_4 <100	52		33		9		10	
CD_4 <50	37		21		10		6	
Ca (mmol/l)	92	2.27	50	2.28	19	2.29	23	2.25
Mg (mmol/l)	91	1.04	49	1.11	19	0.94	23	1.00
PO_4(mmol/l)	91	2.46	49	2.49	19	1.99	23	2.80
Uric acid (mg/dl)	10	0.60	4	0.70	3	0.57	3	0.49
Blood Culture S.pneumonia	5		3		1		1	
Staphylococcus	2		0		0		2	
MRSA	4		3		1		0	
E.Coli	3		2		1		0	
Salmonella	2		2		0		0	
Urine leucocytes+	58		32		13		13	
erythrocytes +	40		20		10		10	
Urine PCR	67	0.61	31	0.24	18	0.58	18	1.25
Urine E.Coli	9		4		3		2	
K.pneumonia	4		3		1		0	
Conservative	25		7		5		13	
Survived	43		28		10		5	
Died	33		22		6		5	

Comparison of Acute kidney injury Appendix 4

*Characteristics		HIV positive	HIV negative	p
Number		50	90	
Age (years)	mean	37.42	45.20	ns
Sex	male	28 (56)	55 (61)	ns
	female	22 (44)	35 (39)	ns
Race	Black	49 (98)	67 (74)	0.0004
	White	1	15 (17)	
	Coloured	-	2	
	Indian	-	6	
Wards	Medical	37 (74)	43 (48)	0.0022
	Surgical	4 (8)	22 (24)	
	ICU	6 (12)	15 (17)	
	Gynae	3 (6)	10 (11)	
Aetiology	sepsis	31 (62)	39 (43)	
	haemodynamic	10 (20)	15(17)	
	toxin	5 (10)	6 (7)	
	urological obstruction	4 (8)	7 (8)	
	miscellaneous	5 (10)	21 (23)	
Hypertension		2 (4)	19 (21)	ns
Diabetes		2 (4)	13 (14)	ns
Tuberculosis		13 (26)	2 (2)	<0.0001
Dialysis		18 (36)	35 (39)	ns
				ns
Renal size (cm)	Right kidney	12.11	10.96	<0.0001
	Left kidney	12.21	11.24	<0.0001
Electrolytes				
Na (mmol/l)		132	139	<0.0001
K (mmol/l)		4.9	4.5	0.0426
Cl^-(mmol/l)		98	103	0.0121
CO_2(mmol/l)		14.7	19.4	0.0002
Urea (mmol/l)	admission	34.5	23.3	0.0013
Creatinine (µmol/l)	admission	619	455	0.07
Calcium (mmol/l)		2.28	2.33	ns
Magnesium (mmol/l)		1.09	0.93	ns
Phosphate (mmol/l)		2.49	1.78	0.0004
Haemoglobin (g/dl)		10.02	10.84	ns
Albumin (g/dl)		27.17	28.58	ns
Hepatitis B		2		
Urine PCR		0.26	0.28	ns
Survived (%)		56	52	0.694
Died (%)		44	47	0.7173