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THE UNIVERSITY OF THE WITWATERSRAND

DEGREE OF MASTERS OF MEDICINE IN INTERNAL MEDICINE

RENAL OUTCOME IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTED PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

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A research report submitted in partial fulfillment of the requirements for the degree of Masters of Medicine in Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

Johannesburg, 2015

DECLARATION

I, Dr. Frank Sinyiza, hereby declare that this research report is my own work. It has not been submitted before for any publication, or degree at any other university. It is submitted to the degree of Master in Internal Medicine of the University of the Witwatersrand, Johannesburg, South Africa.

Signature ----------

Date ---------- 2015

DEDICATION

To my parents, Mr. Watson (RIP) and Mrs. Christina Sinyiza for their guidance and encouragement, my beloved wife Leah for her love and support, my lecturers for their mentorship

ABSTRACT

BACKGROUND:

Renal dysfunction is an increasingly recognized co-morbidity among HIV-infected patients on HAART. Progression to end stage renal disease impacts negatively on morbidity and mortality. I evaluated factors for the development and progression of renal disease, and estimated the incidence and prevalence of CKD stage 3 or worse at an HIV clinic in Johannesburg.

METHODS:

A retrospective study was conducted involving two cohorts of HIV-infected adults on HAART attending Themba Lethu Clinic in Johannesburg, South Africa, from June 2010 to May 2012. The first cohort, the incident cohort, involved patients initiated on HAART between June 2010 and May 2012 with normal baseline renal function. The primary outcome from this study cohort was doubling of serum creatinine from baseline or development of end stage renal disease. The second cohort (prevalent cohort) analysis included HIV-infected patients on HAART during the period under study. Patient data was extracted from Therapy Edge, an electronic database.

RESULTS:

From the incident cohort, 2424 patients met entry criteria, of whom 93 (3.8%) developed renal dysfunction after initiation of HAART, with an incidence of acute renal disease and chronic kidney disease of 2.9% and 0.9% respectively. A total of 28 (1.2%) patients developed either end stage renal disease requiring dialysis or doubled serum creatinine from the baseline. The mean

duration for development of end stage renal disease or doubling of serum creatinine was 10.21 months (range of two weeks to 38 months).

From the prevalent cohort, 2500 HIV-infected adults met the inclusion criteria, of whom 58 had CKD, with a prevalence of 2.3% (95% CI 0.02- 0.03).

Male sex, hypertension, low body mass index, low CD4 count and TDF based regimen were predictors of decline in renal function.

CONCLUSION:

Doubling of serum creatinine or development of end stage renal disease after initiation of HAART was an uncommon finding and the overall incidence and prevalence of chronic kidney disease was low. Screening for evidence of renal dysfunction in HIV-infected patients and treatment of traditional risk factors for CKD are still important for preventing further renal damage.

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LIST OF ABBREVIATIONS

ACE-I	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
AER	Albumin excretion rate
AIDS	Acquired immune deficiency syndrome
ADQI	Acute Dialysis Quality Initiative
AKD	Acute kidney disease
AKI	Acute kidney injury
APOL 1	Apolipoprotein 1
ARF	Acute renal failure
BMI	Body mass index
CD4	Cluster of differentiation 4
CG	Cockcroft-Gault
CHRU	Clinical HIV Research Unit
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

CrCl	Creatinine clearance
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
HAART	Highly active antiretroviral therapy
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy
IC	Iothalamate clearance
IFN-γ	Gamma interferon –γ
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
MDRD	Modification of Diet in renal Disease
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Protein creatinine ratio
RIFLE	Risk of renal dysfunction, injury to the Kidney, Failure or Loss of kidney function, and End-stage kidney disease

SOP	Standard operating procedure
TDF	Tenofovir disoproxil fumarate
TNF- α	Tumour necrosis factor- α
TLC	Themba Lethu Clinic
UNAIDS	United Nations Programme on HIV/AIDS
USA	United States of America
USRDS	United States Renal Data Systems
WT-1	Wilms tumor-1

CHAPTER ONE

1.1 INTRODUCTION AND BACKGROUND OF THE STUDY

Nephropathy is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests, or imaging studies[1]. It has become an important co-morbidity among Human Immunodeficiency Virus (HIV) infected patients whose presentation can be acute renal disease (ARD) or chronic kidney disease (CKD)[2]. Studies demonstrate that African Americans are at greater risk of developing ESRD than their white counterparts in the USA[3,4]. It has been further demonstrated that HIV-associated nephropathy (HIVAN) among blacks between the ages of 20 and 64 years is a third leading cause of end stage renal disease[4]. The estimated prevalence of HIVAN is 3.5% among African-Americans living with HIV[5]. In pre-Highly Active Antiretroviral Therapy (HAART) era, HIVAN was characterized by rapid deterioration of renal function and ESRD requiring dialysis. With the availability HAART, there has been significant reduction in the burden as well as deaths associated with HIV infection[6-8].

Tenofovir disoproxil fumarate (TDF) is a widely prescribed antiretroviral medication in patients living with HIV with 70% of the patients initiated on TDF based regimen[9]. In a retrospective study conducted between April 2004 and September 2009 in Johannesburg, showed that in 890 HIV-infected patients initiated on TDF, 21(2.4%) experienced nephrotoxicity {was defined as any decline in kidney function from the baseline (acute or chronic) that is secondary to toxins including drugs}[10].

Appropriate management and prompt referral of patients with early renal disease depends on identification of renal dysfunction by the physician. Serum creatinine level is routinely used as a screening test to assess renal function[11-13]. However, in clinical trials, ESRD or doubling of serum creatinine from baseline, and death are commonly used endpoints[14]. Doubling of serum creatinine is a commonly used endpoint because it reflects a sustained change in renal function, and predicts patients who may develop ESRD. It is conveniently used as a surrogate endpoint for progression of renal disease[14].

I conducted a retrospective cohort study to evaluate risk factors for reaching renal end points among HIV-infected patients on HAART at Themba Lethu Clinic (TLC), Helen Joseph Hospital, Johannesburg in South Africa. Data was obtained from Therapy Edge, an electronic database. The incidence and prevalence of chronic kidney disease was also estimated among HIV-infected patients on HAART.

1.2 Problem statement

HIV remains a burden in Southern Africa region, including South Africa. About 6% of people living with HIV in South Africa develop chronic kidney disease (CKD)[15]. Even with HAART, CKD remains a problem among patients living with HIV with prevalence varying from 3.3% to 8.4% according to several studies[16-18]. Renal dysfunction can be caused directly by HIV infection itself, co-infections, co-morbidities, toxic effects of antiretroviral therapy, or opportunistic infections and their treatments as well as other co-morbidities such as hypertension and diabetic mellitus[19]. Progression to ESRD impacts negatively on morbidity and mortality.

1.3 Significance of the study

Despite potential benefits of antiretroviral therapy on survival of patients with kidney disease, progression to ESRD still occurs[20]. The ability to predict renal outcome and take appropriate interventions such as identifying and screening for CKD among those at risk, and treatment of co-morbid conditions may slow the progression of kidney dysfunction and delay the onset of renal failure[21].

The main aim of the study is to look at the incidence and prevalence of CKD stage 3 or worse in HIV infected patients on HAART, and evaluate risk factors associated with the development of renal disease.

1.4 LITERATURE REVIEW

1.4.1 HIV Burden

At the end of 2010, about 34 million people were living with HIV worldwide, which represents an increase of 17% from 2001[22]. Majority of these HIV-infected patients (68%) were living in sub-Saharan Africa[22].

In South Africa, the estimated total number of HIV-infected patients increased from 4.1 million in 2001 to 5.24 million by 2010 representing 10.5% of the total population[23]. The estimated prevalence of HIV in Gauteng province is 10.3%[24]. Among all the provinces, Gauteng has the fifth largest number of people living with HIV after Kwazulu Natal, Mpumalanga, the Free State and North West provinces[24]. Over 1 million people living with HIV are estimated to be on HAART in South Africa with Gauteng province having the second largest number of patients on HAART, with over 207,000 estimated to be treated at various sites by end of March 2010[25].

1.4.2 HIV infection and kidney disease

HIV infected patients are at risk of developing either acute renal dysfunction or CKD. In assessing patients with renal dysfunction, it is important to distinguish acute kidney disease from chronic kidney disease as this may have an impact on management.

1.4.2.1 Acute kidney disease (AKD)

AKD is defined as acute kidney injury (AKI) or GFR<60ml/min per 1.73m2 for <3 months or decrease in GFR by >35% or increase in serum creatinine by >50% for < 3months or structural kidney damage for <3months[26]. While AKI is defined as an abrupt (within 48 hours) reduction in kidney function based on an elevation in serum creatinine level, a reduction in urine output, the need for renal replacement therapy (dialysis), or a combination of these factors[27].

AKI is a common finding among people living with HIV and is associated with advanced stages of HIV infection as well as traditional risk factors for AKI, such as old age, diabetes, pre-existing CKD and hepatitis co-infection[28,29]. In a prospective study conducted among 754 ambulatory HIV-infected patients, of whom 61% were blacks, reported an incident rate of acute kidney injury of 5.9 per 100 person-years[29]. However, in hospitalized patients, an incidence of 14.8% has been reported among HIV-infected patients using RIFLE criteria for AKI, a decline from 18% as previously reported[30, 31].

In 2004, the Acute Dialysis Quality Initiative (ADQI) workgroup developed a classification system for AKI abbreviated RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease) as shown in Table 1.1[32]. RIFLE is increasingly used in research[32].

Table 1.1: Classification for acute kidney injury (AKI) using RIFLE criteria

Category	GFR Criteria	Urine Output (UO) Criteria
Risk	Increased creatinine x1.5 or GFR decrease > 25%	Urine output < 0.5ml/kg/h x 6 hr
Injury	Increased creatinine x2 or GFR decrease > 50%	Urine output < 0.5ml/kg/h x 12 hr
Failure	Increase creatinine x3 or GFR decrease > 75%	Urine output < 0.3ml/kg/h x 24 hr or Anuria x 12 hrs
Loss	Persistent ARF = complete loss of kidney function > 4 weeks	
ESRD	End Stage Renal Disease (> 3 months)	

ARF, Acute Renal Failure.

1.4.2.2 Chronic Kidney Disease (CKD)

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health[26]. Criteria for definition of CKD according to 2012 KDIGO guidelines is as shown below in Table 1.2.

Table 1.2: Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER >30 mg/24 hours; ACR >30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

The US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) published its classification of five stages of chronic kidney disease based on GFR in table 1.3[33]:

Table 1.3: Stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	>90
2	Mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure	< 15 or dialysis

1.4.3 HIV- related CKD burden in Africa

Unlike in developed countries, chronic kidney disease is 3–4 times more common in Africa[34]. CKD is among the important potential chronic complication of HIV in sub-Saharan Africa[35]. Studies have also demonstrated that HIV-associated nephropathy (HIVAN) is more common among HIV-infected patients of African descent[36].

1.4.3.1 Apolipoprotein L1 (APOL 1) and risk

Studies have identified specific genetic variants within the APOL1 gene as a major contributor to these ethnic differences, rather than MYH9 gene on chromosome 22 as previously thought[37,38]. The G1 and G2 variants of APOL 1 are predominately found in people of African descent[38]. Studies show that these variants are believed to be responsible for the disparities in rates of ESRD observed between black patients and white patients[38,39].

The APOL 1 variants are fatal to Trypanosoma brucei rhodesiense, a parasite that causes African sleeping sickness, conferring a survival advantage to carriers[40]. Thus there is an increased prevalence of these variants in affected populations (predominately in Southern and East Africa).

APOL1 normally cause glomerulosclerosis by various mechanisms[41]. It associates with high-density lipoprotein (HDL) particles in the circulation, and the APOL 1 variants may bind less tightly to the circulating HDL, undergo glomerular filtration and proximal tubular resorption, thereby causing kidney disease. Renal disease may also be caused by circulating APOL1 variant

proteins, either free in circulation or bound to HDL which may be filtered by the kidney[42]. Endogenous APOL1 in the renal epithelium-like cell may cause apoptosis or autophagic cell death[43]. APOL1 variants have the capacity to induce podocyte injury which is further augmented by adverse host factors such as hydrogen peroxide, hypoxia, tumour necrosis factor-α, and puromycin aminonucleoside[44]. HIV-1 infected cells release cytokines such as IFN-γ and TNF- α that promote APOL-1 expression in endothelial cells[45].

Studies demonstrate that the absence of risk alleles strongly predicts lesions other than Focal Segmental Glomerulosclerosis (FSGS). About 76% of those with biopsy-proven FSGS carried two risk alleles[46]. However, there is no direct role of the APOL1 risk variants in the pathogenesis of HIV-associated immune complex glomerulonephritis[46].

1.4.3.2 Other risk factors

This racial predilection for ESRD in HIV infection is consistent with the epidemiology of ESRD in the general population, for which the risk of progression from CKD to ESRD has been reported as 4-fold higher in blacks compared with whites[47]. The risk of ESRD in persons infected with HIV appears to be due to traditional risk factors associated with CKD such as hypertension, cardiovascular disease, diabetes, dyslipidaemia, as well as HIV disease severity[48]. Markers of HIV disease severity include a CD4 cell count of less than 200 cells/µL and a high viral burden[48]. A retrospective study of 22,156 people living with HIV without pre-existing ESRD showed that patients with low CD4 counts (less than 200 cells/µL) incurred a 50% increase in

ESRD risk, whereas those with CD4 lymphocyte counts of 200-350 cells/µL did not have increased risk[48]. Similarly, having a HIV viral load of more than 30,000 copies/mL, hepatitis C co-infection or hypoalbuminemia each were associated with a 2-fold increase in ESRD risk[48].

1.4.4 HIVAN

In pre-HAART era, HIVAN was characterized by acute deterioration of kidney failure and end stage renal disease requiring dialysis. Antiretroviral therapy has reduced the morbidity and mortality associated with HIV infection, as well as leading to a substantial decline in HIVAN[49,50].

A case study of a 28 years old HIV-1 positive African American with HIVAN requiring haemodialysis showed that a few months after starting HAART, dialysis was not required, and serum creatinine and proteinuria improved[51].

HIVAN is characterized by worsening renal disease, usually associated with proteinuria and enlarged, echogenic kidneys on ultrasound scan[52].The pathogenesis of HIVAN may be due to direct HIV-1 infection of epithelial cells in the kidneys with resultant expression of nef and vpr genes which induce podocyte dysfunction and apoptosis of renal epithelial cells in genetically predisposed individuals[53,54]. In HIVAN, podocytes exhibit a dysregulated phenotype {loss of regulatory protein Wills tumor-1 (WT-1)} characterized by increased proliferation, apoptosis and dedifferentiation[53,54,55]. Podocytes in HIVAN also have reduced expression of synaptopodin and

WT-1 while the expression of desmin, which forms part of intermediate filaments is increased. The expression of WT-1 down-regulates proliferation[56].

The commonest histological finding in HIVAN is a collapsing variant of FSGS [57,58]. Diagnosis of HIVAN is based on the presence of the following typical features on renal biopsy; focal segmental glomerulosclerosis in its collapsing variant, absence of immune deposit by immunofluorescence and tubules with microcystic changes and proteinaceous casts in the lumen[58]. However, HIV seropositive individuals may present with a variety of other glomerular lesions such as arterionephrosclerosis, pyelonephritis, interstitial nephritis, diabetic nephropathy, IgA nephropathy, cryoglobulinemia, amyloidosis, a lupus like immune complex glomerulopathy and HIV-associated thrombotic microangiopathy [58, 59,60].

Renal biopsy is required for differentiating HIVAN from other diseases responsible for kidney disease. Indications for renal biopsy in patients with HIV infection may include significant proteinuria, evidence of progressive disease, unexplained acute renal failure or an acute nephritic syndrome[61].

1.4.5 Effects of drugs on renal function

1.4.5.1 HAART

HAART has resulted in significant decline in HIVAN, however, HAART may directly induce for kidney dysfunction[62]. Most of these drugs are metabolized and excreted by the kidney.

Studies have shown that major predictors of eGFR decline in patients on HAART are hypertension, hyperlipidaemia, proteinuria, use of tenofovir or stavudine and higher viral load[63]. Several antiretrovirals are associated with renal dysfunction thus it is important to monitor renal function and adjust the dosage based on eGFR.

The South African Antiretroviral Treatment Guidelines of 2010 and those updated in 2013, recommend the use of a combination of three antiretroviral agents which including nucleoside/nucleotide reverse transcriptase inhibitors and a non nucleoside reverse transcriptase inhibitor as a first line regimen or two reverse transcriptase inhibitors plus protease inhibitor as second line[64,65]. TDF nephrotoxicity predominantly occurs in patients with underlying kidney disease, the elderly, with prolonged use, an elevated baseline creatinine, African American ethnicity, CD4 <200cells/μL and concomitant administration of nephrotoxic drugs[66].

If TDF is combined with protease inhibitors such as lopinavir/ritonavir the risk of renal toxicity increases. Protease inhibitors indirectly cause renal toxicity by increasing TDF concentrations in plasma and renal tubular epithelium, thereby increasing the risk of TDF toxicity, because they decrease renal clearance of TDF by 17.5%, by inhibiting its transport across renal tubules[67,68]. Patients with low-body weight may have high TDF concentrations, therefore they are at increased risk of kidney impairment[69]. The most common manifestation of TDF nephrotoxicity is proximal tubular dysfunction, sometimes causing Fanconi's syndrome which is characterized by proximal tubular acidosis, hypophosphatemia, hypouricemia, glycosuria in absence of hyperglycemia, and proteinuria[69].

Diagnostic criteria of TDF nephrotoxicity are based on evidence of TDF use at the time of presentation, histological findings of mitochondrial tubulopathy, an acute renal dysfunction without alternative causes of acute decline in renal function[70]. The outcome after discontinuation of TDF is good, however, a small number of patients continue to have impaired renal function for more than 6 months after TDF discontinuation[71].

1.4.5.2 Other drugs

Several non-antiretroviral drugs such as amphotericin B, pentamidine and acyclovir, may cause renal toxicity [72]. These drugs are usually used in the treatment of opportunistic infections.

1.4.6 Screening for renal disease

The importance of prevention of CKD in HIV-infected individuals should not be underestimated. Screening for renal diseases in HIV infected individuals has been recommended in high risk groups for CKD such as individuals of black ethnicity, those with diabetes, hypertension, hepatitis C virus co-infection, CD4 cell counts less than 200 cells/mm^3, or HIV RNA levels greater than 4000 copies/Ml[73]. Baseline screening tests at initial HIV documentation may include urine analysis for proteinuria, serum creatinine with eGFR[73]. If baseline screening tests are abnormal, then further investigations such as urine protein-creatinine ratio (urine PCR) and renal ultrasound should be performed. Those who are at risk of developing CKD with normal baseline screening tests should be rescreened annually[73].

1.4.6.1 Determining GFR

The gold standard methods for determining GFR include inulin and iothalamate clearance (IC), but these tests are expensive, time-consuming, highly dependent on collection accuracy and thus not routinely performed in clinical practice[74,75]. Serum creatinine concentration is the most frequently used test of renal function because of its availability and affordability. Furthermore, creatinine clearance (CrCl) or eGFR can be easily estimated from serum creatinine levels and other variables[76]. However, serum creatinine is not a reliable estimate of GFR because its concentration is affected by several factors such as age, weight, muscle mass, race, various medications and extraglomerular elimination. Studies demonstrate that among patients with creatinine levels within normal range, between 11.6% (108 out of 928 patients) and 15.2% (387 out of 2543 patients) were found to have decreased GFR[77-80].

In clinical practice, creatinine-based equations, such as the Cockcroft-Gault (CG), the Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are commonly used to evaluate kidney function[81-83].

Halving of GFR assessed as doubling of creatinine level has been accepted by The US Food and Drug Administration as a surrogate endpoint for development of kidney failure[84]. Halving of kidney function sustained over a period of time will likely proceed to dialysis or renal transplantation and thus is felt to reflect a sustained reduction in GFR and hence progression to ESRD[85 86].

1.4.7 Conclusion

Renal disease is an important co-morbid condition among HIV-infected patients. It occurs in a wide clinical spectrum which includes potentially reversible AKD and CKD. Causes of nephropathy are diverse and usually multifactorial. Several factors are associated with renal disease which include traditional risk factors for CKD, HIV disease severity, HAART and nephrotoxic drug use. In post HAART era, there has been reduction in morbidity and mortality associated with HIV infection as well as reduction in HIVAN. A variety of glomerular lesions may be found on histological examination but HIVAN remains common among black Africans[87,88]. Measurements of proteinuria and eGFR are important in assessing renal function. In clinical trials doubling of serum creatinine, ESRD, and death are commonly used end points.

CHAPTER TWO

2.1 OBJECTIVES

2.1.1 Broad objective

To evaluate the relevance of defined variables that may be associated with the development and progression of renal disease in HIV-infected individuals on HAART attending Themba Lethu Clinic in Johannesburg from June 2010 to May 2012.

2.1.2 Specific objectives

1. To evaluate factors associated with doubling of serum creatinine as a marker of significant renal damage or the development of end stage renal disease in HIV-infected patients on HAART.

2. To determine the mean duration for doubling of serum creatinine or developing end stage renal disease.

3. Describe the incidence and prevalence of CKD stage 3 or worse in HIV-infected patients on HAART at an HIV clinic in Johannesburg.

2.2 RESEARCH DESIGN AND METHODOLOGY

2.2.1 Population and study sample

This was a retrospective cross-sectional study conducted at Themba Lethu Clinic (TLC). TLC is the biggest government antiretroviral treatment site in South Africa. The clinic is situated at Helen Joseph Hospital in Johannesburg. About 30,000 HIV-infected patients have been enrolled into the HIV care and treatment programme since its inception in April 2004, with over 21,000 patients initiated on HAART[9]. The majority of the cohort at the clinic are of African ethnicity (93%) and are predominately female (64%)[9].

TLC follows the National HAART Treatment Guidelines. Patients are seen at least every 3 months. Serum creatinine level is taken at baseline, three months, six months then yearly if the patient is on TDF, so as to detect TDF toxicity. Data fields collected routinely at TLC include demographic, clinical visit, laboratory, medication and clinical data as shown in Table 2.1[9].

Table 2.1: Data fields collected routinely on patients at TLC

Data fields	Variable list
Demographics	Name, national ID number, contact details, gender, date of birth, employment status, alcohol use, smoking history, ethnicity and education level
Clinical visit data	Date of visit (scheduled and actual), TB screening, urine analysis, vital signs, height, weight, description and duration of new symptoms and systems-based clinical examination (e.g. cardiology, neurology, and respiratory)
Laboratory results	ART initiation and monitoring bloods, including CD4 count, HIV viral load, full blood counts, liver function tests, renal function tests, TB microscopy and culture results, lactate levels and glucose and lipid profiles
Medication history	Date of start and stop of ART and non-ART medications, reasons for treatment discontinuation and self-reported treatment adherence
Clinical diagnoses	Pregnancy, opportunistic infections including TB, hepatitis, PCP, AIDS-related malignancies including Kaposi sarcoma, ART toxicities including peripheral neuropathy, anaemia, hyperlactataemia/ lactic acidosis and lipoatrophy

2.2.2 Study population

In this study, about 5,000 HIV-infected persons on HAART attending TLC between June 2010 and May 2012 were targeted. The study population was divided into incident and prevalent cohorts. Patients were screened from the data base to identify those with documented HAART use. The target for each cohort was 2,500 HIV- infected patients.

2.2.2.1 Incident cohort

These patients were initiated on ART between June 2010 and May 2012, were greater than 18 years of age, had documented baseline weight, height, CD4 count and serum creatinine recorded prior to initiation of HAART and had been followed up at the clinic after initiation of HAART with laboratory monitoring of renal function for at least 6 months. These patients had normal renal function (eGFR >60 mL/min/1.73 m^2 at initiation of HAART). Patients with missing demographic information and baseline blood tests were excluded from the study.

On each patient, the following information was obtained; gender, age, ethnicity, body mass index, blood pressure and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin B, acyclovir, aminoglycosides and ACE inhibitors which may be potentially nephrotoxic drugs. The use of antiretroviral medications such as tenofovir based regime with or without protease inhibitors including other regimens were recorded. Laboratory data including serum creatinine, eGFR was obtained (Appendix 1).

2.2.2.2 Prevalent cohort

To describe the burden of CKD, 2500 patients who were on antiretroviral therapy during the period under study (regardless of when they were started on HAART) were targeted. This included patients who were initiated on HAART before June, 2010 and those who were started on HAART between June 2010 and May 2012. The baseline demographic information obtained

included sex, age, race as well as BMI. Two consecutive measures of eGFR taken at least three months apart were obtained (Appendix 2).

2.3 Data Sources and Management

Patient data was extracted from Therapy Edge, an electronic database after fulfilling the Clinical HIV Research Unit (CHRU) Standard Operating Procedure (SOP). Data was managed using Excel and SPSS.

2.4 Definition of Study Variables

i) Hypertension:
   - Was defined as blood pressure greater than 140/90 mmHg on three separate occasions[89], or use of antihypertensive medications.

ii) TDF based regimen was defined by documentary evidence of TDF use, while TDF use with protease inhibitor was defined as use of TDF with either indinavir or lopinavir/ritonavir.

iii) Nephrotoxic drug use was defined as documented use of NSAID, amphotericin B, acyclovir, aminoglycosides and/or ACE (angiotensin-converting-enzyme) inhibitors.

iv) Gender was defined as male or female.

v) Body mass index (BMI): Was calculated as weight in kilograms divided by the square of height in meters: underweight, normal weight, and overweight were defined as BMI less than 18.50kg/m^2, BMI between 18.5kg/m^2- 24.99kg/m^2 and BMI ≥25.0kg/m^2 respectively.

vi) Elderly was defined as patients greater than 65 years of age.

vii) Ethnicity was defined as black or other races.

viii) High viral load was be defined as viral load >30,000 copies/ml[48].

ix) CD4 count nadir was defined as CD4 count less than 200 cells/µL[29].

x) Doubling of serum creatinine was defined as two fold increase in serum creatinine from baseline.

xi) Normal renal function was based on eGFR >60 ml/min per 1.73 m^2.

xii) Acute Kidney Disease (AKD) was defined as GFR <60 ml/min per 1.73 m^2 for <3 months[26].

xiii) CKD stage 3 or worse was defined as two consecutive measures of GFR <60 ml/min per 1.73 m^2 over ≥ 3 months.

xiv) ESRD was defined as CKD stage 5.

2.5 Evaluation of renal function

Renal function was evaluated using serum creatinine and eGFR. eGFR was calculated by using 4-variable Modification of Diet in Renal Disease (MDRD) formula as shown below[81]:

eGFR (ml/min/1.73 m^2) = 175 × {[plasma creatinine (μmol/l) / 88.4] $^{-1.154}$} × age (years) $^{-0.203}$ × 0.742 (if female).

2.6 CKD

Patients with eGFR of less than 60 ml/min/1.73 m^2 were categorised as having renal dysfunction while measurement of eGFR over a 3-month or greater period was used to establish CKD stage 3 or worse. At least two consecutive readings of eGFR 3 or months apart were used to define CKD in prevalent population. Proteinuria is a marker of progression of CKD. It can be evaluated by measurement of urine albumin-to-creatinine ratio (ACR) and urine protein-to-creatinine ratio (PCR)[26].

2.7 Variable Outcome

The primary variable outcome was doubling of serum creatinine from the baseline, or development of end stage renal disease (ESRD). Trends were analysed from their baseline serum creatinine before initiation of antiretroviral therapy. Doubling of serum creatinine was defined as

a twofold increase in serum creatinine concentration from baseline while ESRD was defined as CKD stage 5.

2.8 Statistical Analysis

Statistical analysis included descriptive, bivariate and multivariate analyses. Characteristics of all laboratory tests done were entered in excel sheet as well as patients' demographic characteristics, nephrotoxic drugs and HAART regime.

To measure the association between explanatory variables and outcome variable for categorical values, Pearson Chi-Square and Fisher's Exact Test were used for analysis. Binary linear logistic regression was used to establish the risk associated with defined variables to development of variable outcome. A value of $p<0.05$ was set to be statistically significant with confidence interval of 95%. All p-values were two tailed.

Population data for the period under study constituted the denominator for CKD incidence and prevalence estimations. For numerators new cases, and new and old cases, were used to calculate incidence and prevalence respectively. Analysis was performed using SPSS statistics 19.

2.9 Ethical Consideration

Ethical clearance to conduct the study was obtained from the Human Research Ethics Committee (Medical) of University of the Witwatersrand (Appendix 3). Permission to conduct the study was

also sought from the Regulatory Manager at the CHRU, Department of Internal Medicine, Helen Joseph Hospital (Appendix 4). Patients were not directly involved in the study as data was obtained from an electronic data base. Confidentiality was respected as no patient identifiers were used in data collection, analysis and reporting.

CHAPTER THREE

3.0 RESULTS

3.1 Incident cohort

A total of 2,424 out of 2,500 HIV-infected patients who were started on HAART between June 2010 and May 2012 were included for study analysis, 76 patients did not meet inclusion criteria for the study because they were either missing baseline information or had impaired renal function prior to initiation of HAART. There were 1,564 females (64.5%), the median age was 36.8years (range 18 – 69years) years with majority of the patients being Africans (black) (94.9%), Table 3.1.

Among patients with recorded BMI, 10.6% were underweight, 41.5% had normal weight while 24.3% were overweight with BMI of < 18.5kg/m^2, 18.5kg/m^2 to 24.9kg/m^2 and > 25kg/m^2 respectively.

TDF based regimen was the commonly prescribed first line regimen at initiation (76.5%). Among the study cohort, 68.1% had a CD4 nadir of <200 cells/ µL at initiation but only 3% of the patients had their viral load test done prior to initiation of HAART.

The proportion of hypertensive patients among this study group was 23.7%. Only 6.5% of the patients were recorded as having a history of nephrotoxic drugs use.

Of 2,424 patients with normal baseline renal function, 93 (3.8%) developed renal dysfunction (eGFR less than 60 ml/min/1.73m^2 based on eGFR estimation using MDRD equation) after initiation of HAART. Of 93 patients with renal dysfunction, 70 (2.9%) developed ARD after initiation of HAART while 23 developed CKD stage 3 or worse, representing an incidence of 0.9% (Figure 1).

Across the entire cohort, 28 (1.2%) developed either ESRD or doubled serum creatinine from the baseline after initiation of HAART. When these data were stratified for the use of a specific antiretroviral, there was strong correlation between doubling of serum creatinine and use of a tenofovir based regimen (p=0.039). Patients with a low BMI were more likely to double serum creatinine than those with normal weight (p=0.012). There was also a positive correlation between CD4 count and development of ESRD or doubling of serum creatinine with a p= 0.044. There was no significant relationship between sex, hypertension, the use of nephrotoxic drugs, and the development of ESRD or doubling of serum creatinine.

Proteinuria is an important marker of kidney disease, but this was not recorded in the data base at the clinic therefore no results were available for analysis.

Significant variables were further analysed using a linear logistic regression model as shown in Table 3.2.

The mean duration for the development of ESRD or doubling of serum creatinine was 10.21 months with a range of two weeks to 38 months.

Table 3.1: Incidence cohort showing baseline characteristics and bivariate analysis of factors associated with renal dysfunction and doubling of serum creatinine or development of end stage renal disease

		Frequency	Bivariate			
Characteristic		n^1 = 2424	Renal dysfunction		ESRD or Doubling of serum creatinine	
			n^2=93 (3.8%)	p-value	n^3=28 (1.2%)	p-value
Demographics						
Sex	Female	1564 (64.5%)	47		15	
	Male	860 (35.5%)	46	0.004	13	0.223
Race	Black African	2301 (94.9%)	90		27	
	Other races	123 (5.1%)	3	0.627	1	1.000
Age in years	Median	36.8(range 18.2-69)				
	< 65	2399 (99.0%)	90		28	
	≥ 65	25 (1.0%)	3	0.068	0	1.000
HIV related factors						
HAART Regimen	1 (TDF based)	1855 (76.5%)	65		22	
	2(TDF+ Lopinavir)	54 (2.2%)	3		0	
	3 (Lopinavir with other)	32 (1.3%)	2		2	0.039
	4 (other)	483 (19.9%)	23	0.455	4	
CD4 nadir at initiation of HAART(cells/uL)	< 200	1651 (68.1%)	78		24	
	≥ 200	773 (31.9%)	15	0.001	4	0.044
Viral load at initiation of HAART (copies/ml)	≥ 30,000	72 (3%)	3		1	
	< 30,000	5 (0.2%)	0		0	
	Missing	2347 (96.8%)	90	0.815	27	1.000

Table 3.1: (Continued)

		Frequency	Bivariate			
Characteristic		n^1 = 2424	Renal dysfunction		ESRD or Doubling of serum creatinine	
			n^2=93 (3.8%)	p-value	n^3=28 (1.2%)	p-value
Concurrent medical conditions and drug use						
Baseline BMI(kg/m^2)	<18.5 (underweight)	257 (10.6%)	11		6	
	18.5to24.9 (normal)	1007 (41.5%)	40		12	
	>25.0 (overweight)	588 (24.3%)	22		1	0.012
	Missing	572 (23.6%)	20	0.931	9	
Hypertension	Yes	574 (23.7%)	34		8	
	No	1791(73.9%)	59	0.005	20	0.593
	No	521 (90.8%)	31		6	
Nephrotoxic use	Yes	157 (6.5%)	7		2	
	No	2267 (93.5%)	86	0.675	26	0.702

n^1, total number of HIV infected patients on HAART

n^2, renal dysfunction after initiation on HAART

n^3, Variable outcome, doubling of serum creatinine or development of end stage renal disease

Figure 1: Flow diagram of incident cohort

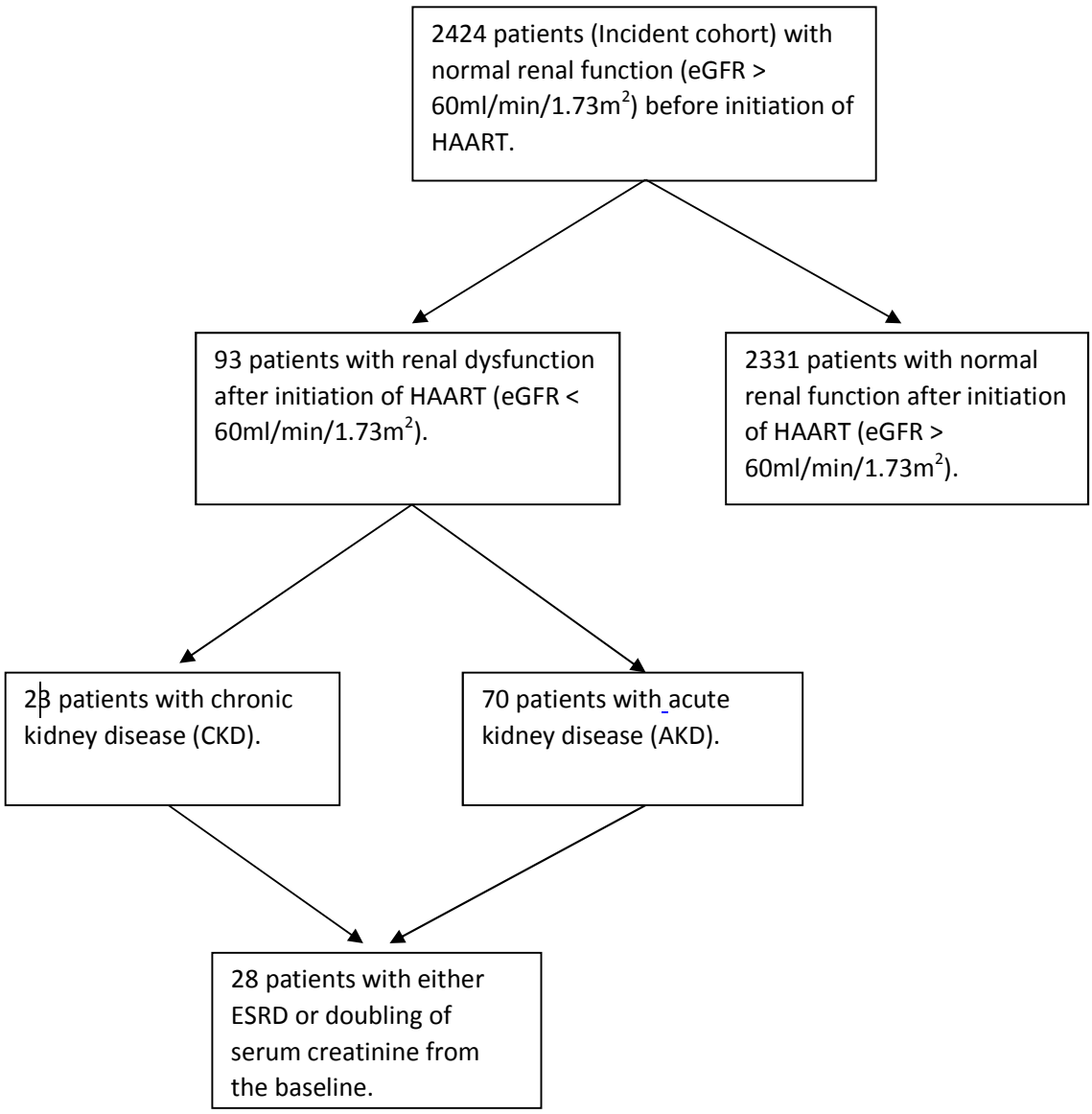


Table 3.2: Incident cohort showing Multivariate logistic regression of explanatory variables associated with doubling of serum creatinine or development of end stage renal disease.

Variable	Odds ratio	95% confidence interval
HAART Regimen	0.989	0.715-1.369
CD4 <200 cells/uL	2.825	0.771-8.218
HAART Regimen	1.215	0.850-1.737
Baseline BMI	0.358	0.176-0.727
Baseline BMI	0.376	0.184-0.768
CD4 <200 cells/uL	2.910	0.665-12.727

3.2 Prevalent Cohort

Of the 2,500 HIV-infected patients on HAART, the median age was 36.3years (range: 18 – 70years), 66.9% were female, 97% were black African, were included for analysis as shown in Table 3.3.

The results show that 34.5% of the patients were on TDF based regimen lower than the incident group (76.5%). Among patients with a recorded BMI, 12.3% were underweight, 48.2% had normal weight while 23.6% were overweight

Across the cohort, 58 patients had CKD stage 3 or worse representing a prevalence of 2.3% (95% CI 0.02 - 0.03).

Of all patients with CKD stage 3 or worse, 44 (75.9%) had a moderate reduction in eGFR (30-59 mL/min/1.73 m^2), 8 (13.8%) had a severe reduction in Egfr (15-29 mL/min/1.73 m^2) and 6 (10.3%) had ESRD (eGFR less than 15 mL/min/1.73 m^2) as shown in Figure 2.

Similarly to the incident cohort, there was unfortunately no recording of proteinuria in the TLC database.

In multivariate model, the risk factor for CKD were TDF based regimen and low BMI (Table 3.4).

Table 3.3: Prevalent cohort showing baseline characteristics of CKD stage 3 or worse

VARIABLE		Number (n=2500)	CKD n=58 (2.3%)	CKD stage		
				3	4	5
Sex	Female	1672 (66.9%)	23	19	2	2
	Male	828 (33.1)	35	25	6	4
Ethnicity	Black or African	2424 (97%)	51	43	8	6
	Other races	76 (3.0%)	1	1	0	0
HAART Regimen	1 (TDF based)	862 (34.5%)	5	5	0	0
	2 (TDF + Lopinavir)	35 (1.4%)	1	1	0	0
	3 (Lopinavir with other)	104 (4.2%)	0	0	0	0
	4 (other)	1499 (60%)	52	38	8	6
Baseline BMI(kg/m^2)	< 18.5 (under weight)	307 (12.3%)	11	7	4	0
	18.5 to < 25.0 (normal)	1204 (48.2%)	21	16	3	2
	≥ 25.0 (overweight)	589 (23.6%)	16	14	1	1
	Missing	400 (16%)	10	-	-	-

Figure 2: Stages of CKD in prevalent cohort

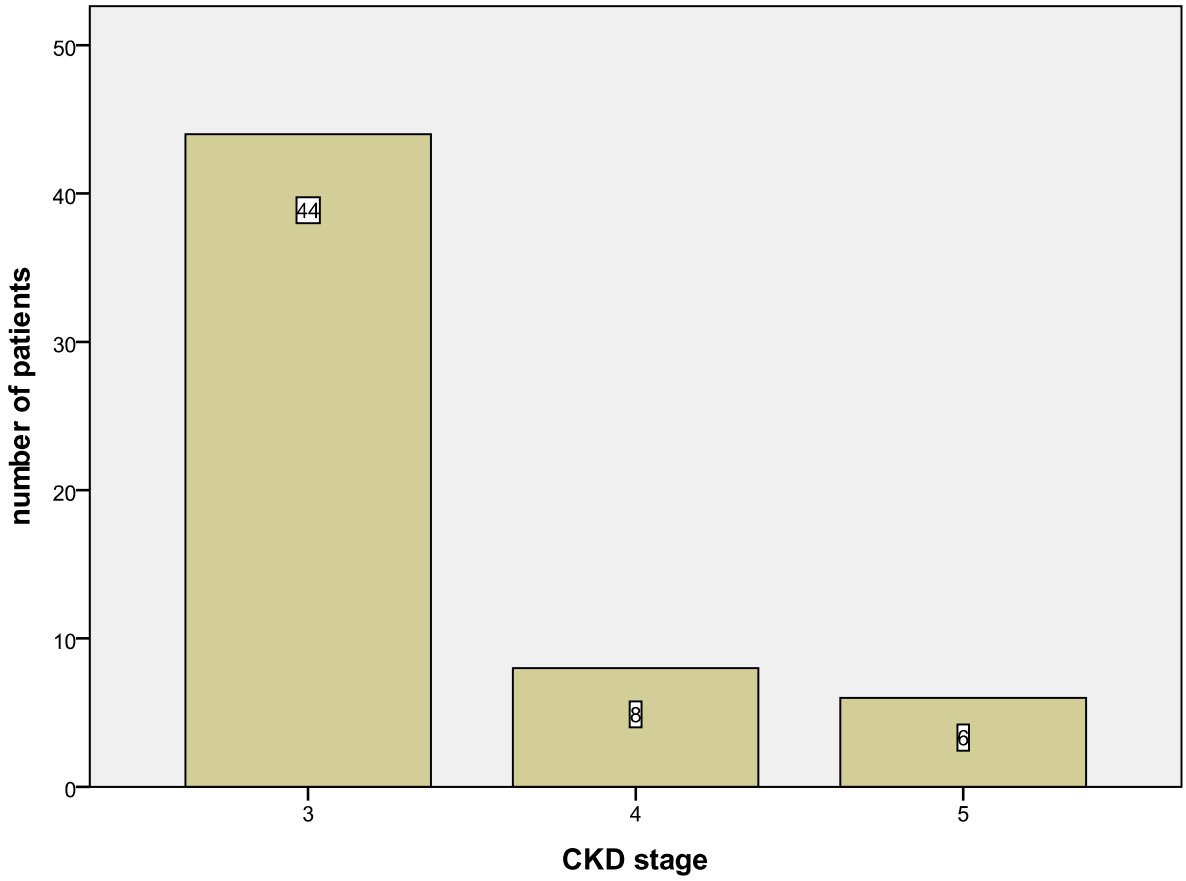


Table 3.4: Prevalent cohort showing multivariate logistic regression of factors associated with CKD stage 3 or worse in the prevalent cohort

Variable	Odds ratio	95% confidence interval	p-value
HAART Regimen	1.981	1.384-2.835	<0.05
Body Mass Index (BMI)	0.978	0.623-1.535	0.92
Body Mass Index (BMI)	1.182	0.737-1.895	<0.05
Sex	3.608	1.958-6.645	<0.05
Sex	3.378	1.977-5.771	<0.05
HAART Regimen	1.877	1.386-2.542	<0.05

CHAPTER FOUR

4.1 DISCUSSION

4.1.1 Incident cohort

The important endpoint of this study was doubling of serum creatinine or development of ESRD. From this study cohort, ESRD or doubling of serum creatinine after initiation of antiretroviral therapy was infrequent. Factors associated with doubling of serum creatinine or development of ESRD in HIV-infected patients initiated on HAART included CD4 nadir <200 cells/uL, TDF based regimen and low body mass index.

Regarding lower CD4 nadir count, the study findings were consistent with other studies showing that HIV-patients with low CD4 are at more risk of developing kidney disease independent of other risk factors[48]. Early diagnosis and treatment of HIV-infected patients would avoid occurrence of low CD4 counts thus possibly preventing additional kidney disease.

High viral load, a marker of advanced HIV disease, is associated with an increased risk of renal dysfunction[48]. However, in this study, there was no significant difference in doubling of serum creatinine or development of ESRD among individuals with viral load > 30,000copies /ml or <30,000 copies/ml. The possible reason for this may be explained by fewer patients 77 (3.2%) who had a viral load test done prior to initiation of HAART.

This study showed no significant difference in the development of ESRD or doubling of serum creatinine among HIV-infected patients older or younger than 65 years. This is in contrast with other studies that have demonstrated that old age is a risk factor for the development of renal

dysfunction[66]. This inconsistent finding may be attributed to the fact that my study cohort was predominately younger than 65 years of age with only 1% of the cohort older than 65years.

The study findings showed that was no difference in development of ESRD or doubling of serum creatinine with respect to patient ethnicity, however the cohort was predominantly of black African origin. This is in contrast to the data reported from other studies that demonstrated that CKD in people living with HIV is more prevalent in black populations and are more likely to progress to ESRD[36,47].

The study findings show that there was a statistical difference in patients with hypertension and those who developed renal dysfunction which was consistent to other reported data[63]. However, there was no association between hypertension and ESRD or doubling of serum creatinine from baseline.

The findings of this study demonstrate that there was strong correlation between doubling of serum creatinine or development of ESRD and TDF based regimen which was consistent to other reported data that decline in renal function was associated with TDF use[10,62]. However, studies show that discontinuation of TDF may lead to recovery of renal dysfunction[10, 71]. In a study conducted predominantly among Caucasians and African Americans, showed that the female gender, black race, and a CD4 count of <200 cells/uL were factors associated with renal dysfunction after initiation of tenofovir[57]. It was noted that the use of nephrotoxic drugs was not significantly correlated with doubling of serum creatinine or development of ESRD. This is discordant with other studies that demonstrated that use of nephrotoxic drugs or therapy factors are related to decline in eGFR[72].

The mean duration for doubling of serum creatinine or development of ESRD was 10.2 months with a range of two weeks to 38 months. Studies have shown that more than 50% of patients develop acute renal disease within three months after commencement of HIV care (such as antiretroviral therapy and prophylaxis against opportunistic infections) and incidence of AKD decreased more than 10-fold in patients who had been on HIV care for more than three months[90]. This demonstrates that HIV-infected patients are at risk of developing renal dysfunction regardless of the duration they have been on HAART.

Out of the 2,424 patients with normal baseline renal function, 93(3.8%) developed renal dysfunction (defined as GFR < 60ml/mim/1.73m^2) after starting HAART with an incidence of AKD of 2.9%. This is lower than 14.8% reported in hospitalized HIV-infected patients[30]. This was expected as hospitalized patients are more likely to have other co-morbidities that may contribute to renal dysfunction. The findings of the study showed that male sex, low CD4 and hypertension were predictors of renal dysfunction which is consistent with data reported from other studies [26,28,91].

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The incidence of CKD stage 3 or worse among incident cohort was 0.9%. The incidence of CKD was low which was consistent with that found in other studies (1.5 per 100 person years and 1.45 per 100 person years)[92,93].

4.1.2 Prevalent cohort

The prevalence of CKD stage 3 and among the prevalent cohort was 2.3%. The prevalence is lower than that previously reported in South Africa (6%) but was consistent with that published in other study (2.4%)[15,94] . The possible reason for this may be due to improved access to HIV services leading to reduction in nephropathy attributable to advanced HIV infection.

In the prevalent cohort, predictors associated with development of CKD included lower CD4 nadir, the use of a TDF based regimen, and low BMI which is consistent with previous studies[48,63,69]. Studies have shown that there is marked racial predilection for development of chronic kidney disease in blacks compared to other races[35, 36]. Evaluation of racial differences as possible risk factor for development of CKD stage 3 or worse was not conducted because the study's cohort was predominately black (97%).

This study further demonstrated that CKD stage 3 or worse was more prevalent in patients on a TDF based regimen then other regimens. This is concordant with other studies which demonstrate that tenofovir use is a potential risk factor for renal impairment.

Studies have shown that patients who concomitantly used tenofovir and a lopinavir boosted protease inhibitor had a significant deterioration in kidney function as opposed to those who received other regimens such as non-nucleoside reverse transcriptase inhibitors with tenofovir[67, 68,95]. However, this was not demonstrated in this study possibly due to the small number of patients (1.4%) that were on a TDF and protease inhibitor based regimen.

From this study, it was noted that ESRD was uncommon among patients with CKD stage 3 and worse. Of 58 patients with CKD, only 6(10.3%) had CKD stage 5.

4.2 LIMITATION OF THE STUDY

The study had several limitations which include

- It was a retrospective study.
- Some patients had missing data.
- Proteinuria was not looked at because it was not recorded in the database.

4.3 CONCLUSION

The doubling of serum creatinine from the baseline or development of ESRD, as the primary end point, after initiation of HAART was an uncommon finding in the incident cohort. Renal dysfunction, although uncommon, was seen to occur at any time during the course of antiretroviral therapy. The overall incidence and prevalence of chronic kidney disease was low, supporting the current change in the epidemiology of kidney disease in post HAART era with fewer causes of nephropathy due to HIV disease severity. Among patients with renal dysfunction, decline in estimated GFR more attributable to traditional risk factors for CKD, TDF based regimen and low CD4 count.

Screening for evidence of renal dysfunction among patients on antiretroviral therapy and treatment of traditional risks factors for CKD is important for preventing further renal damage.

4.4 Disclosure statement

There are no conflicts of interest.

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Appendix 1: Incident cohort data collection sheet

Demographics		
Sex	Male	
	Female	
Age in years	<65	
	≥65	
Race	Black African	
	Other races	
Concurrent medical condition and drug use		
BMI(Kg/m^2)	<18.5(underweight)	
	18.5to24.9(normal)	
	>25.0(overweight)	
Hypertension	Yes	
	No	
Nephrotoxic drug use	Yes	
	No	
HIV related factors		
CD4 nadir at initiation of HAART(cells/uL)	<200	
	≥ 200	
Viral load at initiation of HAART (copies/ml)	<30,000	
	≥ 30,000	
HAART Regimen	TDF based	
	TDF+ Lopinavir	
	Lopinavir with	

	Other combination	
	Other	
Baseline serum creatinine mmol/l		
Serum creatinine after initiation of HAART		
Baseline eGFR		
eGFR after initiation of HAART		
End point (ESRD or doubling of serum creatinine from the baseline)	Yes	
	No	
Duration in weeks of reaching end point		

Appendix 2: Prevalent cohort data collection sheet

Demographics		
Sex	Male	
	Female	
Age in years	<65	
	≥65	
Race	Black African	
	Other races	
Concurrent medical condition		
BMI(Kg/m^2)	<18.5(underweight)	
	18.5to24.9(normal)	
	>25.0(overweight)	
Renal function (first and second eGFR taken at least 3 months apart)		
eGFR	First	
	Second	
CKD stage 3 or worse	Yes	
	No	

Appendix 3: Ethical clearance certificate from Human Research Ethical Committee (Medical)

R14/49 Dr Frank Sinyiza

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130827

NAME: (Principal Investigator)	Dr Frank Sinyiza
DEPARTMENT:	Internal Medicine Themba Lethu Clinic/Helen Joseph Hospital
PROJECT TITLE:	Renal Outcome in Human Immunodeficiency Virus (HIV) Infected Patients on Highly Active Antiretroviral Therapy (HAART)
DATE CONSIDERED:	30/08/2013
DECISION:	Approved uncodntitionally
CONDITIONS:	
SUPERVISOR:	Dr Graham Paget and Dr William B MacLeod
APPROVED BY:	pp _____ Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/08/2013 (Initial approval)20/04/2015(Recertified)

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

_____ 20th April 2015

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 4: Letter of permission from Themba Lethu Clinic, Helen Joseph Hospital

Themba Lethu Clinic Helen Joseph Hospital, Pvt Bag X 47, Auckland Park

GAUTENG PROVINCIAL GOVERNMENT

CHRU Themba Lethu

10 July 2013.

To whom it may concern.

Re: Frank Sinyiza – Renal outcomes in HIV infected patients on HAART.

This serves to confirm that the above mentioned has been granted permission to conduct his study at Themba Lethu clinic, Helen Joseph Hospital.

We are pleased as the findings of this study will be shared with the clinic and the lessons learned may be implemented for the benefit of the patients.

Regards.

Dr I Motloung.
Medical Manager

Motloung

2013 -07- 10

Appendix 5: Letter of approval from Faculty of Health Sciences

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax:
Tel: 011 7172040

Reference: Ms Mpumi Mnqapu
E-mail: mpumi.mnqapu@wits.ac.za

29 July 2013
Person No: 368959
PAG

Dr FW Sinyiza
Kamuzo Central Hospital
PO Box 149
Lilongwe
0265
Malawi

Dear Dr Sinyiza

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Renal outcome in HIV infected patients on HAART* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences