

**Outcomes of HIV-positive
Patients with Renal Insufficiency
on treatment with HAART at
Charlotte Maxeke Johannesburg
Academic Hospital**

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Declaration

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

Presentations arising from this study

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Abbreviations

ACE-I = Angiotensin-converting-enzyme inhibitor

ADAMTS13 = Adisintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

AIDS = Acquired Immunodeficiency Syndrome

AKI = Acute kidney injury

APOL1 = Apolipoprotein L1

ART = antiretroviral therapy

CCR5 = C-C chemokine receptor type 5

CD4 = Cluster of differentiation 4

CIN = Chronic interstitial nephritis

CKD = Chronic kidney disease

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

CXCR4 = Chemokine receptor type 4

eGFR = estimated Glomerular filtration rate

ESRD = End stage renal disease

FSGS = Focal segmental glomerulosclerosis

GN = Glomerulonephritis

gp120 = Glycoprotein 120

HAART = Highly Active Antiretroviral Treatment

HIV = Human Immunodeficiency Virus

HIVAN = HIV-associated nephropathy

HIV-ICD = HIV-associated immune complex disease

HUS = Haemolytic-uraemic syndrome

Ig = Immunoglobulin

IL = Interleukin

MDRD = Modification of Diet in Renal Disease

MHY9 = Non-muscle myosin heavy chain 9

nef = Negative regulatory factor

NF-B = Nuclear factor kappa-light-chain-enhancer of activated B cells

NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor

NRTI = Nucleoside Reverse Transcriptase Inhibitor

PCR = Protein: creatinine ratio

PI = Protease Inhibitor

rev = Regulator of expression of virion proteins

RRT = Renal replacement therapy

tat = Trans-activator of transcription

TB = Tuberculosis

TDF = Tenofovir

TMA = Thrombotic microangiopathy

TNF = Tumour necrosis factor

TTP = Thrombotic thrombocytopaenic purpura

vif = Viral infectivity factor

vpr = Viral protein R

WHO = World Health Organization

1. INTRODUCTION AND LITERATURE REVIEW

With the increasing use of Highly Active Antiretroviral Treatment (HAART), renal disease is becoming an increasingly important consideration in the course of the disease. According to UNAIDS estimates, 35 million people were living with HIV at the end of 2012. Sub-Saharan Africa bears the largest burden of the disease with 25 million people (approximately 69%) living with the disease. The number of children and adults in sub-Saharan Africa receiving antiretroviral therapy (ART) is steadily increasing, with 56% of those eligible now receiving treatment. With scaling up of treatment in recent years, AIDS-related deaths have decreased by 24% compared to 2005.¹ Changes in the WHO guidelines for eligibility for antiretroviral therapy (ART), including CD4 counts of below 350 cell/ μ L, will result in a larger number of people living with HIV/AIDS and the complications thereof.² In resource-limited settings like sub-Saharan Africa, predictors of outcome are becoming increasingly important in the decision to initiate HAART. Renal disease is an independent risk factor for progression to AIDS and overall mortality.

1.1 Prevalence of Chronic Kidney Disease in HIV infection

The worldwide prevalence of chronic kidney disease (CKD) in HIV patients has been difficult to ascertain due to a paucity of data, especially from developing countries. A cross-sectional study done across 33 countries in Europe revealed that the prevalence of CKD using the Cockcroft-Gault formula to estimate glomerular filtration rate (eGFR) was 3.5% and that of the Modification of Diet in Renal Disease(MDRD) formula was 4.7%.³ Kidney disease was defined as the presence of albuminuria and/or low GFR, based on serum creatinine measurements. In sub-Saharan Africa prevalence rates range between 6% and 45%.⁴ Varying degrees of prevalence have been found in studies done across

Africa. In a study done in Zambia of 25 779 patients started on ART, 33.5% were found to have renal insufficiency (measured by serum creatinine at baseline). Risk of mortality was also shown to be elevated at or before 90 days.⁵ A Nigerian study revealed a 38% prevalence of renal disease in HIV positive patients.⁶ A Rwandan study showed a lower prevalence with 2.4% of patients with a low eGFR and 8.7% with proteinuria.⁷ A study performed in Malawi revealed a high prevalence of renal impairment in patients with WHO early clinical staging of HIV (stages I and II), measured by proteinuria (23.3%) and abnormal serum creatinine (57.4%).⁸ In a study in Johannesburg on the incidence of urinary abnormalities on dipstick testing in ART-naïve patients, 30% had leucocyturia, 33% had microscopic haematuria and 44% had microalbuminuria/ proteinuria.⁹ These studies suggest that the prevalence of kidney disease is high and point to the importance of screening for chronic kidney disease in all HIV-positive patients.

In a study conducted at Chris Hani Baragwanath hospital in Johannesburg, 99 ART-naïve in-patients were biopsied and 27% revealed HIV-associated nephropathy (HIVAN), 21% HIV-associated immune complex disease (HIV-ICD) and 13% membranous nephropathy. The rest had features of nonglomerulonephritic renal disease, post infectious or mesangioproliferative glomerulonephritis and IgA nephropathy.¹⁰ In a study done at King Edward VII Hospital in Durban with 615 HIV positive ART-naïve outpatients, 6% had persistent proteinuria; 37 of these patients with persistent proteinuria were biopsied, 30 were found to have histology in keeping with HIVAN (83.3%). Other conditions detected were HIVAN combined with membranous glomerulonephritis, membranous glomerulonephritis and interstitial nephritis.¹¹ Differences in results could be attributed to the high degree of genetic variability among black South Africans and patient selection.¹² A study performed in the United States with 89 patients who were biopsied showed that 42 had HIVAN, 13 immune complex glomerulonephritis, 8 with membranous glomerulopathy, 6 with diabetic nephropathy, 5 with membranoproliferative glomerulonephritis. The remainder showed interstitial nephritis,

amyloid, focal segmental glomerulosclerosis, minimal change disease, IgA nephropathy and chronic pyelonephritis. In this study, patients with renal disease other than HIVAN did not seem to benefit from the use of ARTs and viral suppression and additional therapeutic strategies were needed.¹³ A study from Groote Schuur hospital in Cape Town showed that those with HIVAN as well as immune complex glomerulonephritis improved with therapy. The study also highlighted various subtypes of HIVAN, different histological associations and their differing responses to HAART.¹⁴ These studies show the wide range of histological results in patients with clinical renal disease and the differing responses seen to treatment. This suggests that renal histology will improve management of HIV patients with renal disease.

1.2 Risk factors for developing HIV-associated kidney disease

Several studies have pointed to HIV infection being an independent risk factor for microalbuminuria. A study done in the United States showed 11% of HIV positive patients had microalbuminuria. It was found that the odds were 5 times higher for those with HIV to have microalbuminuria than control patients. Predictors for albuminuria in HIV patients included lower CD4 count, higher viral load and African-American race.¹⁵ In another study, older age, black race, hepatitis C infection and lower CD4 count were independently associated with chronic kidney disease. Of note virological suppression was also more common with renal impairment, most likely due to higher blood levels of renally eliminated ARTs.¹⁶

HIVAN was described as a disease entity over 20 years ago, found predominantly in the African-American population in the United States. It is currently the third leading cause of end-stage renal failure in this group between the ages of 20-64.¹⁷ An association has been shown between the APOL1 gene on chromosome 22 (seen in African Americans) and FSGS and hypertension-attributed

end-stage kidney disease. It is thought this gene in Africa contributed as a survival factor to those infected with *Trypanosoma brucei rhodesiense*.¹⁸ A subsequent study revealed 17 fold higher odds for FSGS and 29-fold higher risk for HIVAN in those with the APOL1 variant. Untreated HIV positive patients with the APOL1 risk allele have a 50% risk for developing HIVAN.¹⁹ Genetic variations at the MYH9 locus had previously been reported to be associated with increased risk of FSGS in the African American population.²⁰ Additional risk factors for HIVAN includes low CD4 count (<200 cells/ μ L), high HIV viral load (>4000 copies/mL) and family history of renal disease.¹⁶

Other risk factors for the development of proteinuric kidney disease in this subset of patients includes co-morbid diseases such as diabetes mellitus and hypertension. They increase the risk for CKD 10-fold and are becoming increasingly common in HIV infected individuals. In the Multicentre AIDS Cohort Study the prevalence of diabetes mellitus was 14%, which was 4 times higher than that of the seronegative control group. It was found to be linked to cumulative exposure to nucleoside reverse-transcriptase inhibitors, which are part of first line regimens for ART and are commonly included in most regimens given to patients. In the same study, the prevalence of hypertension was 3 times higher than in the control group. These results point to the importance of optimizing blood pressure and glycaemic control in order to minimize the impact of CKD concomitant with HIV infection.

1.3 Pathogenic effects of Viral Infection on the Kidney

1.3.1 HIV Virus Infection of Renal Cells

The question of whether HIV directly infects renal cells is an issue central to pathogenesis. CD4 and chemokine receptors which are needed for viral entry are not typically expressed on these cells therefore viral replication is likely restricted. Viral products are produced by renal epithelial cells when viral constructs are transfected. Cell expression of CXCR4 and CD4 chemokine receptors allow

viral replication. It is still unclear how HIV-1 enters renal cells.²³ Genetic variability of gp120 seems to influence renal infectivity. Lymphocytes possibly permit cell infection in a monolayer via transcytosis. Another possible mechanism is transfer of CCR5 between cells (these have cytoplasmic and cell surface components of the original cell), thus allowing entry of the HIV virus into renal cells without endogenous expression of the co-receptor. Dendritic cells have been found to play a part in binding, dissemination and transfer of the virus in different tissues and may also play a role in infection of renal cells. DEC-205 (the dendritic cell C-type lectin receptor) has been found to assist entry of the virus into renal tubular cells. Therefore there is increasing evidence to suggest that renal cells may support viral replication.²⁴

1.3.2 Viral proteins

Studies in transgenic mice expressing viral proteins have suggested that *vpr* and macrophage-specific expression of HIV proteins may play a role in the evolution of FSGS. Some suggest that *nef* may affect the severity of interstitial nephritis, but not the glomerular changes seen in HIVAN.²⁵

Podocyte-restricted expressions of *vif*, *nef*, *tat*, *vpr* and *rev* have been shown to induce many of the features of HIVAN in mice models.²⁶ In HIVAN specimens, apoptosis of renal epithelial cells mediated by caspase activation and *Fas* up-regulation has been seen.²³

1.3.3 Changes in Renal Microvasculature

A recognized feature of HIV infection includes deposition of platelets and thrombi in the vessel wall and endothelial dysfunction caused by abnormalities of the clotting cascade. How HIV affects renal vasculature is important in understanding the pathogenesis of thrombotic microangiopathy (TMA) and other HIV-associated renal diseases. Expression of TNF and interleukin-1 is up-regulated in HIV infection of the kidney. This further drives renal inflammation and can contribute to changes in regulation of the clotting cascade. *Fas*-mediated apoptosis of endothelial cells is triggered by HIV

proteins. Down-regulation of von Willebrand factor is a primary component of TMA by antibodies against the ADAMTS13 protease.²⁷

1.3.4 Host Factors

As mentioned before, genetic variations such as the APOL1 and MYH9 variants have been found to have a strong association with HIV kidney disease in African-Americans.

It has been suggested that through activation of cytokine pathways disease phenotype could affect the host response to viral infection. It has been shown that up-regulation of many genes which mediate the inflammatory response in renal epithelial cells such as chemokines, cytokines and adhesion molecules occur in patients with HIV-associated renal disease. A number of such up-regulated genes are targets of NF- κ B and IL-6. TNF and IL-6 expression by tubular and mesangial epithelial cells increase HIV-1 expression by entering monocytes and further driving cytokine production. The part played by inflammatory mediators in the pathogenesis of HIVAN is not yet entirely understood.²⁸

Chronic HIV infection is associated with high levels of immunoglobulins. It is suggested that immune complexes circulating in the systemic circulation are deposited in the microvasculature of the kidney, leading to HIV immune complex kidney diseases.²⁹

1.4 Detection of renal disease

1.4.1 Renal function

Renal function is determined using various methods. In patients with lower relative muscle mass (e.g., older patients, women, and patients with low body weight due to cachexia or chronic illness), abnormal renal function may not be recognized with serum creatinine alone. eGFR is commonly used and is more accurate. The GFR is defined as the volume of fluid filtered from the glomerular

capillaries into Bowman's capsule per unit time. A number of formulae have been devised to estimate GFR based on serum creatinine levels and other parameters such as age, race, gender and weight. A widely used formula is the Cockcroft-Gault formula, which incorporates age, gender, mass and serum creatinine. A more recently advocated formula is the MDRD formula. This uses the four variables of race, gender, age and serum creatinine. Both formulae have a level of bias and tend to overestimate the GFR. Another recently devised formula is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula which takes into account race, age, gender and serum creatinine. None of the above formulae have been validated for HIV patients. The one that is used more prevalently is the simplified MDRD equation.

1.4.2 Proteinuria

Another marker used to screen for CKD is the level of protein in the urine. Persistent proteinuria of more than 30mg albumin per gram of creatinine in the urine is indicative of CKD. Microalbuminuria is a level of 30-299 mg/g albumin in the urine which is usually not detected by urine dipstick methods. It is associated with abnormal glycosylation in diabetes or systemic processes in other chronic diseases and is a marker of early vessel damage. In HIV positive patients, proteinuria has been associated with a higher risk of CKD, ESRD, AIDS-defining illness and mortality. This relationship seen between proteinuria and these outcomes implies that it may be a sign of diffuse vascular processes which have an effect both within and outside the kidney.¹⁵

1.4.3 AKI and CKD

A vital step in evaluating kidney disease is the differentiation between acute kidney injury (AKI) and CKD. AKI is defined as a clinical syndrome with an abrupt deterioration in GFR over days to weeks. The Acute Kidney Injury Network (AKIN) defines AKI as "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3mg/dL ($\geq 26.4 \mu\text{mol/l}$), a percentage increase in serum creatinine of more than or equal to 50%

(1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5ml/kg per hour for more than six hours).”²¹

Chronic kidney disease has been defined as evidence of kidney damage that persists for 3 months or more.²² The stages of chronic kidney disease are shown in the table below.

Table 1. Stages of chronic kidney disease

Stage	Description	GFR, mL/min per 1.73m ²
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)

Note: Reproduced with the kind permission of the National Kidney Foundation. Adapted from *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002, 39:1-266*

As seen in the table, estimates of GFR using the C-G or MDRD equation are used to grade renal function. ESRD is defined as stage V CKD. To screen for early CKD, guidelines mention the importance of measuring “spot” urinary albumin and/or protein to creatinine ratios.

Acid-base and electrolyte disturbances are commonly found in HIV positive hospitalized patients, many of which are drug-induced.¹²

1.5 Clinical Spectrum of HIV-related Kidney Disease

Table 2 below shows a summary of the clinical syndromes of HIV-related kidney disease and their causes.

Table 2. Clinical syndromes of HIV-related kidney disease

Clinical syndrome	Features	Clinical assessment	Specific causes
Glomerular syndrome	Nephrotic syndrome: proteinuria + haematuria ± hypertension	First: viral-related diseases Then, drug-related diseases	HIVAN in blacks; MPGN in whites; HIVICK; lupus-like nephropathy; HBV, HCV coinfection; PIGN Foscarnet; interferon; enfur tide
Tubular syndrome	Acute kidney injury, Fanconi syndrome (proximal tubular injury), diabetes insipidus, crystal nephropathy	Drug-related diseases	Aminoglycosides; foscarnet; tenofovir; didanosine; amphotericin; indinavir; ciprofloxacin; intravenous acyclovir
Interstitial nephropathy	Tubular proteinuria, ± haematuria	First: drug nephrotoxicity Then HIV-related diseases	Indinavir; didanosine; atazanavir; aciclovir; foscarnet; interferon; abacavir HIV-associated interstitial infiltrates; sarcoidosis, Sjögren syndrome; opportunistic infection; IRIS; DILS
Vascular nephropathy	Hypertension ± low-range proteinuria, ± mechanic haemolytic anaemia	First: HIV-related diseases Then: drug nephrotoxicity	HIV-associated TMA; APLS Valaciclovir; interferon

Note: Adapted from Kopp J, Fabian J, Naicker S. *HIV and the Kidney. In Clinical Comprehensive Nephrology 4th edition p 675-686*, with permission from Elsevier.

APLS = Antiphospholipid syndrome; DILS = Diffuse Infiltrative Lymphocytosis Syndrome; HBV = Hepatitis B virus; Hepatitis C virus; IRIS = Immune Reconstitution Syndrome; MPGN = Membranoproliferative glomerulonephritis; PIGN = Post-infectious glomerulonephritis

1.5.1 Acute Kidney Injury

AKI is common in individuals with HIV infection and is linked to increased morbidity and mortality. The risk of in-patient mortality is six-fold higher in ART-naïve patients with AKI.¹² Risk factors include severe immunosuppression (CD4 count < 200cells/ μ L), older age, serious systemic illness or infection, exposure to nephrotoxic agents and pre-existing CKD. Common causes of AKI in this group of patients are sepsis, AKI from drug toxicity associated with treatment of opportunistic infections, herbal ingestion, gastroenteritis with dehydration and TMA.^{4,12} Nephrotoxicity related to ART is another cause of AKI, although its incidence is relatively low. The commonest effects are crystal-induced obstruction secondary to protease inhibitors and proximal tubule damage related to tenofovir. Early recognition of proximal tubule injury in tenofovir-related AKI is important to prevent irreversible chronic tubulointerstitial fibrosis.³⁰ Awareness of possible underlying CKD in patients admitted to hospital with AKI is an important consideration for clinicians treating these patients.¹² In a study of patients admitted with AKI to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), the outcomes for HIV positive and negative patients were similar when given appropriate therapy (including dialysis).³¹

1.5.2 Chronic Kidney Disease

HIV affects the kidney in a number of ways. It can affect either a single or multiple compartments and the effects are highly variable. The importance of initiation of HAART in HIV related kidney disease has been stressed, as these patients are at increased risk of rapid deterioration of renal function to ESRD. Even with HAART, CKD is associated with an increased progression to AIDS and death. Anaemia is more severe in HIV-associated ESRD and these patients are at increased risk of

renal osteodystrophy. Dyslipidaemia associated with HAART and proteinuric renal disease leads to a higher risk of cardiovascular disease. Studies have reported an increased association between microalbuminuria and cardiovascular risk factors (increased systolic blood pressure and glucose resistance).¹⁵

Many patients with HIV-associated kidney disease present with renal dysfunction and proteinuria/nephrotic syndrome. The only reliable way to determine the cause is by histological diagnosis.

HIVAN has been classified by the WHO as an AIDS-defining illness and therefore the initiation of ART is mandatory irrespective of the CD 4 count. There have been studies which suggest that other HIV-associated kidney diseases do not respond to the same degree to ARTs.¹³ Other reports have shown that some non-HIVAN lesions do respond well to therapy.^{14, 32} It was also seen that certain histological subtypes of HIVAN respond poorly to HAART.¹⁴ This highlights the importance of histological diagnosis in this group of patients, as it has an impact on the outcome of patients.

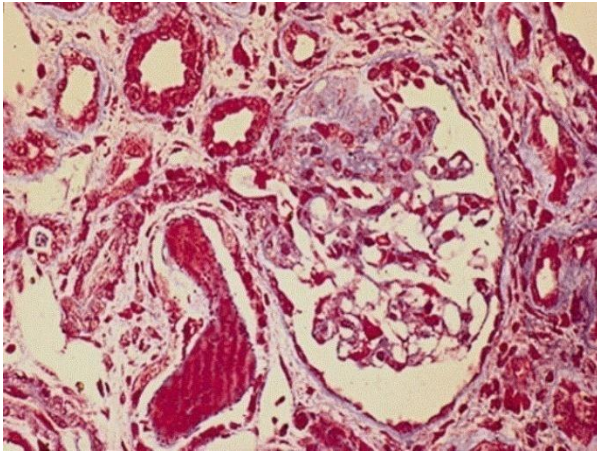
1.5.2.1 HIV-associated Nephropathy

HIVAN is 7-10 times more common in men than woman and is found predominantly in people of African descent. With the introduction of HAART, there has been a decline in deaths from AIDS and the number of black patients living with HIV has markedly increased. Subsequently it is to be expected that the incidence of ESRD secondary to HIVAN will rise as it is this patient demographic which is at risk. Most patients in our setting in sub-Saharan Africa present late with advanced CKD. The delay in detection of HIVAN could be due to a lack of routine initial screening for proteinuria and renal dysfunction.^{33, 34} Another reason is the relative absence of overt signs such as peripheral oedema and hypertension. The only definitive way to establish the diagnosis of HIVAN is by renal biopsy. It has been recommended that renal biopsy be offered to patients with unexplained renal

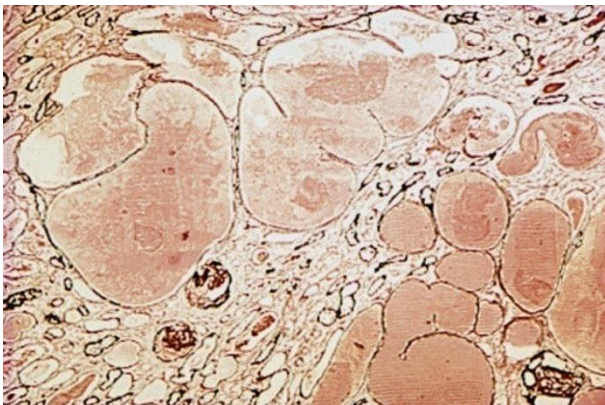
abnormalities (i.e. kidney failure and/or significant proteinuria and/or microscopic haematuria) as the treatment implications and prognosis are influenced by the biopsy results.¹³

Clinical presentation HIVAN is a form of glomerular disease characterized by proteinuria/nephrotic syndrome, focal segmental glomerulosclerosis with collapse of the glomerular tuft and a rapid progression to ESRD within 6-12 months if not treated. Classically the clinical manifestation is that of nephrotic syndrome without peripheral oedema despite severe hypoalbuminaemia. Patients are generally normotensive even though renal insufficiency is present and tend to have hyponatraemia; hence it is thought to be a “salt wasting disease”.³⁵ On ultrasonography they have normal to large size kidneys which are highly echogenic. The study done in Cape Town revealed the clinical correlations of nephrotic range proteinuria, systolic blood pressure <140 and diastolic blood pressure <90, kidney size of 12cm on ultrasound with no peripheral oedema to be 91.3% specific for HIVAN but 15.6% sensitive.¹⁴

Pathology findings “HIVAN is characterized by a constellation of pathologic findings involving glomerular, tubular, and interstitial compartments. Glomerular pathologic findings include focal glomerulosclerosis, with prominent collapse of the glomerular tuft. Tubular disease is characterized by the development of tubular dilatation, accompanied by atrophy and flattening of tubular epithelial cells. There is also prominent lymphocytic infiltration of the interstitium.”³⁵ Tubuloreticular inclusions are also commonly found.³⁸



Light microscopy with trichrome staining showing the collapse of the glomerular tuft, with segmental glomerular and interstitial sclerosis (bluish staining). The renal tubules are dilated and filled with proteinaceous material.



Light microscopy showing prominent microcystic dilatation of renal tubules filled with proteinaceous material; this finding is characteristic of human immunodeficiency virus (HIV)-associated nephropathy, although it may also be observed in chronic glomerulonephritis



Electron microscopy showing a segment of the glomerular basement membrane; foot process effacement (black arrow) and prominent tubuloreticular inclusions (red arrow) are present.

Figure 1 Histological features of HIVAN

Reproduced from <http://emedicine.medscape.com/article/246031-overview> with kind permission from Moro O Salifu, MD, MPH, FACP, State University of New York Downstate Medical Center. Accessed on 19 November 2013.

Treatment of HIV HIV infection itself appears to be a cause of HIVAN; therefore ART is a logical choice for first-line therapy. HIVAN has been classified by the WHO as an AIDS-defining condition and therefore ARTs should be initiated regardless of CD4 count.³⁷ HAART seems to be more effective than monotherapy. A study done on patients with biopsy-proven HIVAN showed that those who received therapy had better renal survival compared to those who did not receive therapy.³⁸ Another study from the US showed slower progression to ESRD with those who received HAART.¹³ HAART has also been thought to decrease the incidence of *de novo* HIVAN. Angiotensin Converting Enzyme Inhibitors (ACE-Is) have been shown in a series of studies to slow the progression to renal failure of proteinuric renal diseases. A study was done on 44 patients with HIVAN on histology and early renal disease who were given the choice of fosinopril. In those who consented, serum creatinine remained stable in the majority of patients. One of the 28 progressed to ESRD after a median follow up of 479.5 days. All those who declined fosinopril progressed to ESRD after a mean of 146 days.³⁹ Another study showed a delay in progression of renal failure in a retrospective cohort of 18 patients with HIVAN.⁴⁰ Current guidelines suggest the initiation of ACE-Is as first line therapy in those with hypertension and proteinuria. A number of studies reported a significant improvement in proteinuria and renal function for HIVAN patients on corticosteroid therapy in the time prior to HAART therapy. Another retrospective study showed an improvement in creatinine clearance over time (+3.32 mL/min), compared with a deterioration (-5.57mL/min) in non-corticosteroid treated patients.⁴¹ Strong evidence supporting the use of prednisone therapy in HIVAN came from a prospective study of 20 patients. They were treated with high dose prednisone (60mg/day) for 2-11 weeks, and then a tapering period of 2-26 weeks. The majority of patients experienced significant improvement in proteinuria and renal function. A number of patients relapsed after therapy was stopped, but improved after re-initiation of treatment.⁴² Owing to the small sizes of the studies, short follow up periods and lack of randomization, there is difficulty in drawing conclusions regarding their use in HIVAN. It has been recommended by the Infectious Disease Society of America

guidelines that patients whose kidney function deteriorates despite HAART, who have no evidence of active infection, could be considered for a short course of corticosteroid therapy.³³

Prognosis Diagnosis of HIVAN is generally late in the course of disease in most patients and many have advanced renal failure on diagnosis. Without treatment, most develop ESRD 1-4 months after the diagnosis is made. Clinical manifestations linked to a higher risk of progressive renal failure is seen in patients with increased proteinuria, elevated serum creatinine level, decreased CD4 count, higher viral load and prior to HAART. Histological features of progression to ESRD and a poor response to ART are a high index of chronic damage with a high percentage of sclerotic glomeruli and chronic damage score >75.^{43,44} As discussed above, treatment with a variety of agents has been found to prolong renal survival. Compared to other patients with ESRD, patients with HIVAN have decreased survival. In a study done on patients requiring chronic renal replacement therapy, those with HIVAN had a 4.74 fold higher risk of mortality when compared to other patients with ESRD from other causes.⁴⁵

1.5.2.2 HIV Immune Complex Disease

HIV-ICD is an immune complex-mediated form of glomerulonephritis, and is the second most common diagnosis obtained from biopsies of patients with CKD. The study mentioned previously done in Johannesburg found that of the 99 HIV patients with renal insufficiency biopsied, 21% had HIV-ICD (the largest group was HIVAN at 27%).¹⁰ Another South African study of 221 patients biopsied in Cape Town showed that 42 had features of both HIVAN and HIV-ICD and 16 had features of HIV-ICD alone.¹⁴ While HIVAN has a strong predilection for black patients, in contrast immune complex glomerulonephritis has been reported mainly in white and Asian patients, although they may also occur in black patients.^{10,14} The clinical profile of the patients was similar to that of HIVAN, although they had less proteinuria and a better serum creatinine and albumin on average.¹⁰

HIV-ICD presents with a variety of histological changes. The renal infiltrate consists primarily of B lymphocytes, in contrast to HIVAN where it is composed mainly of T lymphocytes and macrophages.⁴⁶ The pathogenesis is thought to be associated with the development of polyclonal hypergammaglobulinaemia, thus promoting the circulation of immune complexes which are then passively trapped in the kidney. Activation of inflammatory mediators subsequently occurs which results in secondary renal damage similar to that of lupus nephritis. Another effect is thought to be the in-situ deposition of antibodies binding to HIV viral antigens within the kidney.⁴⁶ *“In the HIVICK group, the predominant histologic pattern included variable mesangial alterations, with identifiable immune deposits within the mesangial and paramesangial regions. In addition, some of the biopsies showed a peculiar and to our knowledge not previously described pattern, in which a varying number of subepithelial immune deposits were seen inducing a peculiar localized 'ball-in-cup' reaction pattern from the basement membrane.”*¹⁰

There have been conflicting reports on the benefit of HAART in patients with HIV-ICD. A study done by Szczech et al found that renal function in patients with lesions other than HIVAN, including immune complex kidney disease did not benefit from ARTs.¹³ Two studies in South Africa showed improvement in renal function with HAART irrespective of renal histology.^{14, 32} Immunosuppressive therapies, such as corticosteroids, to dampen the inflammatory response to these complexes at the level of the kidney have been suggested as possible additional strategies for treatment.⁴⁶

1.5.2.3 Ig A Nephropathy

This is one of the immune-mediated renal diseases seen in HIV positive patients. It is thought to be as a result of immune complexes which contain HIV antigens. It is generally less severe than HIVAN and other variants of HIV-ICD and presents with proteinuria, haematuria and renal dysfunction. One small study done in Canada however, found that IgA nephropathy caused severe renal impairment and heavy proteinuria.⁴⁷ The pathology shows diffuse or segmental mesangial matrix expansion with

proliferative changes. Immunofluorescence demonstrates staining primarily for IgA. Increased serum IgA, detectable serum IgA immune complexes and rheumatoid factor could be seen.

1.5.2.4 Other Glomerulonephritides

Other immune-mediated diseases have been found in HIV positive patients including membranous nephropathy, membranoproliferative glomerulonephritis and post-infectious glomerulonephritis. These are often associated with co-infection with Hepatitis B and/or C viral infection. In the study by Gerntoltz et al, of the 99 patients who were biopsied 13% had membranous nephropathy, 8% post-infectious glomerulonephritis (GN) and 6% membranoproliferative GN. It is not known if the pathogenesis of these is directly related to HIV infection. Explanations could include abnormal immune responses associated with viral infection, or responses secondary to superinfections.¹⁰

1.5.2.5 HIV Thrombotic Microangiopathy

HIV-associated TMA is found in 2 forms: haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). It is typically a feature of chronic infection but can also be seen during acute retroviral syndrome. TMA is rare in comparison with HIVAN, however HIV-related TMA accounts for approximately 35% of TMA cases. It tends to occur more frequently in children and young males. HUS is characterized by microangiopathic anaemia and renal impairment, whereas TTP includes a pentad of microangiopathic anaemia, thrombocytopenia, renal impairment, fever and neurological features. Nephrotic range proteinuria can be seen but is typically less than in HIVAN.²⁷

The pathogenesis of the disease is unknown. It is hypothesized to be due to endothelial cell injury and platelet deposition in the microvessels.²⁷ Other factors include concomitant infections, deficiencies of inhibitors of platelet aggregation, cytotoxins and abnormalities of the coagulation cascade. Heightened expression of tissue-type plasminogen activator and fibroblast growth factor are also thought to play a role. Deficiency in the ADAMTS13 (the protease that cleaves von

Willebrand factor) caused by autoimmune inhibitors or genetic mutations, has also been associated with TTP.⁴⁸ Pathological findings in both forms are the deposition of platelets and fibrin rich thrombi in the glomerular capillaries and arterial microvasculature. Other features include fibrinoid necrosis, intimal oedema, onion-skin lesions and microcystic tubular lesions. The role of HIV-1 remains uncertain. The HIV-1 p-24 antigen has been found in endothelial cells within the spleen of a patient with TMA. The same antigen has also been seen in endothelial cells in the bone marrow and brain of HIV patients without TTP/HUS.²⁷

Prognosis of HIV patients with TMA is poor, with mortality rates of 66-100%.⁴⁹ Treatment for TMA includes plasma infusion and plasmapheresis. Splenectomy is reserved for refractory cases. A South African study suggested that HIV patients respond better to fresh frozen plasma than HIV-negative patients and are less likely to require plasma exchange.⁵⁰ Other therapies such as antiplatelet agents, glucocorticoids and immunoglobulin infusions have been used with variable success. There have been reports describing the beneficial effect of ARTs, but further investigation is needed.²⁷

1.5.3 Co-morbid Diseases

Hypertension and diabetes mellitus are the leading causes of CKD in the general population. They account for 71% of ESRD cases and increase the risk of CKD 10-fold. These two chronic conditions are increasingly common in HIV patients. As mentioned before, in the Multicenter AIDS Cohort Study 14% of patients had diabetes, 4-fold higher than in HIV negative patients. It was linked with cumulative exposure to nucleoside reverse-transcriptase inhibitors. Hypertension was 3 times commoner in study patients than in controls. Hypertension and diabetes was reported in 55% and 20% respectively in a study of 129 HIV positive patients.¹⁶ This underlines the importance of optimizing blood pressure and attaining glycaemic control so as to minimize the impact of CKD in HIV infected patients.⁵¹ Current recommendations for HIV positive individuals with nephropathy are that blood pressure should be controlled to no higher than 125/75 mmHg, with the initial use of ACE-Is or Angiotensin II receptor antagonists in those with proteinuria. Screening recommendations

suggest that if there is no sign of proteinuria initially, patients with an increased risk for the development of proteinuric kidney disease (including those with diabetes mellitus and hypertension) should undergo screening annually.³³

The risk of developing tuberculosis (TB) infection is 20-37 times higher in patients who are HIV positive. Of the 8.7 million new cases of TB diagnosed worldwide in 2011, 13% were HIV positive. The major burden of this falls in sub-Saharan Africa. 0.43 Million deaths worldwide were reported in patients with TB and HIV co-infection.⁵² Due to the high prevalence of co-infection, many patients with HIV-associated kidney disease will be co-infected with TB. There is a paucity of data related to TB and HIV-associated kidney disease, and the impact thereof. One study done in Western Kenya found that a history of tuberculosis was significantly associated with proteinuria.⁵³ Acute kidney injury has been described as part of Immune reconstitution syndrome in TB patients who have been started on HAART. Histological examination of one such patient revealed severe granulomatous nephritis with interstitial infiltrates.⁵⁴ Part of this study aims to determine the incidence and the impact of TB in our patients on outcomes.

1.6 Treatment: outcome and complications

1.6.1 Outcome of patients with HIV-associated kidney disease on HAART

Studies show that although renal dysfunction in HIV patients starting HAART is a predictor of poor outcome, it does respond to ARTs. A study done in Uganda of 508 ART-naïve patients with renal insufficiency at baseline found that after 2 years of HAART, the median creatinine clearance increased significantly (53%).⁵⁵ Another study showed patients with HIVAN on ARTs had better renal survival compared to those who did not receive treatment.³⁸ As mentioned before, there are conflicting reports on HIV-associated kidney diseases other than HIVAN. This implies that earlier

diagnosis of kidney disease and additional therapeutical strategies need to be looked at in these patients to improve their outcome.^{15, 32} Interestingly, Fabian et al found that although there was clinical improvement with introduction of HAART, there was not a corresponding resolution of the histological lesions.³²

1.6.2 Current guidelines for HAART and complications of these drugs

Most HAART regimens used in South Africa use a combination of two nucleoside reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI). With the introduction of numerous HIV therapies, the complications associated with HIV infection have expanded to include changes in metabolism secondary to drug usage. Documented side effects include peripheral insulin resistance, impaired glucose tolerance, lipodystrophy and bone demineralization related to possible mitochondrial dysfunction. In addition to direct nephrotoxicity, long-term use of antiretrovirals could advance the development of CKD through these metabolic complications.⁵⁶ Tenofovir (TDF) has been included as part of the first line regimen in current guidelines, and is being used more commonly. Renal dysfunction was more frequent in a systematic review of 517 patients on TDF. They also found a greater risk of acute renal failure in those receiving TDF. However the clinical effect was small and should not restrict the use of TDF.⁵⁷ A later observational analysis of 3316 patients initiated on ARTs showed severe impairment to be infrequent and differences between eGFRs with various ARTs (TDF, abacavir and nevirapine) to be small. Their findings suggest that in resource limited settings, routine monitoring of serum creatinine may not be mandatory and is unlikely to add benefit for the majority of patients.⁵⁵ A study in Johannesburg found that the incidence of renal dysfunction related to tenofovir was most likely related to prior renal disease and dose adjustment was needed to improve outcomes.⁵⁸

1.6.3 Dosing recommendations

The NRTIs are primarily excreted by the kidneys; therefore reduced dosages are required for those with impaired renal function. Screening for kidney disease prior to initiation of ARTs is recommended by the *HIV Medicine Association of the Infectious Diseases Society of America* with subsequent dose modification for patients with GFRs <60ml/min. Patients that have then been identified with CKD are recommended to have more frequent monitoring of kidney function, toxicity and therapeutic efficacy. Care should be taken not to allow for under-dosage as this may lead to inadequate treatment and contribute to virological failure. The NRTIs are not tightly protein-bound and do not have a high molecular weight and therefore can be easily removed by dialysis. With the exception of abacavir, the NRTIs should generally be administered after dialysis. With the exception of nevirapine and indinavir, the NNRTIs, protease inhibitors (PIs) and fusion inhibitors are primarily excreted by the liver and do not need dose adjustment. These two should be administered after dialysis.³³

Table 3 Dose adjustment of ART in Renal Disease

Creatinine clearance/ GFR		
Drug	10 – 50ml/min	<10ml/min
AZT	Unchanged	300 mg daily
ddl	>60 kg body weight: 200 mg daily <60 kg body weight: 150 mg daily	>60 kg body weight: 100 mg daily <60 kg body weight: 75 mg daily
3TC	150 mg daily	50 mg daily
D4T	15 mg 12-hourly	15 mg daily
ABC	Unchanged	Unchanged
TDF	AVOID	AVOID
PIs	Unchanged	Unchanged
NNRTIs	Unchanged	Unchanged

*Note: Adapted from *Guidelines for antiretroviral therapy in adults. SAJHIVMED 2012, 13(3):124.*

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AZT = zidovudine; ddl = didanosine; 3TC = lamivudine; D4T = stavudine; ABC = abacavir;

TDF = tenofovir; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase

Inhibitor.

2. HYPOTHESIS AND AIMS

2.1 Hypothesis

Renal function in HIV positive patients with chronic kidney disease improves with introduction of ARTs.

2.2 Aims and objectives

This study aims to:

1. Evaluate the outcomes of HIV positive patients with chronic kidney disease with the introduction of HAART over a minimum period of one year, using mortality and improvement in renal function and proteinuria over a one year period or longer.
2. Evaluate the prevalence as well as the impact of common co-morbid conditions such as hypertension, diabetes mellitus, tuberculosis and malignancy on the outcomes of these patients.
3. Examine predictors of outcome in patients with renal insufficiency who are started on HAART.

The main objectives of this study will be to:

1. Assess the outcomes of HIV positive patients with background renal insufficiency to HAART, using mortality and improvement in renal function and proteinuria over a one year period or longer.
2. Investigate the prevalence and impact of common co-morbid conditions such as hypertension, diabetes mellitus, tuberculosis and malignancy.
3. Determine predictors (if any) of outcome.

3. METHODS

3.1 Selection of patients

A retrospective review was performed of 495 files of HIV positive patients attending the Charlotte Maxeke HIV Renal Clinic between 2006 and 2009. Ethics approval was received from the University of Witwatersrand Human Research Ethics Committee (Medical) – clearance number M10416. A total of 169 patients seen at the HIV Renal Clinic with CKD were included in the study. These patients were labelled as CKD using The National Kidney Foundation guidelines (kidney damage that persists for ≥ 3 months). 326 patients were excluded for a number of reasons: these patients were found to have AKI, were not initiated on ART, a minimum of 3 month follow up, results were not found, suffered from unrelated concomitant renal disease (e.g. lupus nephritis, polycystic kidney disease, urological complications), non HIV-related malignancies and renal transplant recipients. Histology results were available for 84 patients. These results were included, regardless of whether the patients were ultimately excluded from analysis of the response to ART. The study population was then divided into two groups. Group 1 ($n=87$) had baseline pre-ART initiation renal function results available. The second group (Group 2) ($n=82$) were on ART prior to being referred to the HIV Renal Clinic. Their underlying renal dysfunction may not have been detected at baseline or they developed renal dysfunction on ART. Results were collected at 3, 6, 12 and 24 months.

3.2 Inclusion criteria

- HIV positive
- On ART
- CKD (defined as kidney damage that persists for ≥ 3 months)

3.3 Exclusion criteria

- AKI
- Not on ART
- Unrelated concomitant renal disease
- Non HIV-related malignancies
- Renal transplant recipients

Demographic data such as age, gender and ethnicity and laboratory variables including serum haemoglobin, serum creatinine and urine protein were collected. Co-morbid conditions such as tuberculosis, hypertension, malignancy and diabetes mellitus were included as well. Kidney function was evaluated using serum creatinine and the MDRD formula and proteinuria. Proteinuria was estimated using urine dipsticks, spot protein: creatinine ratio and microalbumin: creatinine ratio. Renal dysfunction was defined as creatinine clearance $\leq 90\mu\text{mol/l}$ (calculated using the MDRD formula). Proteinuria was defined as ranging from microalbuminuria (microalbumin-to-creatinine ratio 3.4–33.9 mg/mmol) to overt proteinuria (protein-to-creatinine ratio > 0.03 g/mmol). Patients in both groups were on various regimens of ART and response was monitored using CD4 count and, where available, viral load.

3.4 Statistical analysis

Statistical analysis was performed using Stata Software version 8 and Graphpad InStat version 3. Demographics including gender, age and CD4 count were evaluated and compared to ensure there was no bias among groups. The differences in these were calculated using the ANOVA test. Comparison of renal function at different intervals was performed using the Kruskal-Wallis test. The associations of renal insufficiency with other factors were calculated using odds ratios with 95%

confidence intervals (CI). Further calculations of multivariable associations with 95% CIs were performed on the variables that were significant ($p < 0.1$) on univariate analysis. Kaplan-Meier survival analysis was performed looking at 2 year survival post study dates.

4. RESULTS

4.1 Demographic data

As discussed previously, the participants were divided into 2 groups for analysis: those ART-naïve (Group 1) and those already on ART on presentation (Group 2). Table 4 describes the baseline data and Table 5 the outcome data at 12 and 24 months.

Table 4 Baseline data

	Group 1 (ART naïve) n = 87	Group 2 (ART prior to presentation) n = 82
Age Mean ($\pm$SD)	37.8 ($\pm$ 9.2)	41.2 ($\pm$ 11.3)
Sex (% female)	42	42
Race (% black)	100	96
Hypertension (%)	37 (42)	34 (41)
Diabetes (%)	11 (12)	11 (13)
Tuberculosis (%)	28 (32)	25 (30)
HIV-related Malignancies	5 (5)	2 (2)
Serum creatinine μmol/l Median (IQR)	298 (144-667)	171 (119-349)
eGFR (ml/minute/1.73m²) Median(IQR)	20.8 (9-50)	38.9 (20-69)
CD4 count (cell/mm³) Median (IQR)	145 (74-273)	298 (191-371)
Proteinuria (g/day) Median (IQR)	0.3 (0.13-0.78)	0.27 (0.08-0.64)

Table 5 Outcomes at 12 and 24 months

	Group 1	Group 2	
<i>Alive</i>	34	30	
<i>Died</i>	18	15	
<i>Lost to follow up</i>	35	37	
<i>Total</i>	87	82	
GROUP 1			
	Month 0	Month 12	Month 24
<i>Patient number</i>	82	53	43
<i>Median creatinine $\mu\text{mol/l}$ (IQR)</i>	298 (144-667)	162 (87-346)	137 (98.5-359)
<i>Median eGFR (ml/min per 1.73m^2) (IQR)</i>	20.8 (9.2-50)	52.4 (20.1-92.1)	57.7 (17.3-88.9)
<i>Patient number</i>	60	35	18
<i>Median proteinuria (g/day) (IQR)</i>	0.2 (0.13-0.78)	0.11 (0.05-0.53)	0.08 (0.05-0.22)
GROUP 2			
	Month 0	Month 12	Month 24
<i>Patient number</i>	82	53	47
<i>Median creatinine $\mu\text{mol/l}$ (IQR)</i>	172 (69-342)	154 (69-342)	137 (100-516)
<i>Median eGFR (ml/min per 1.73m^2) (IQR)</i>	38.9 (20-69)	46.2 (19-79)	47.3 (11.3-87)
<i>Patient number</i>	42	27	16
<i>Median proteinuria (g/day) (IQR)</i>	0.3 (0.08-0.6)	0.11 (0.03-0.36)	0.21 (0.08-0.4)

Group 1 The mean age was 38 years, 42 (48%) were female, with a median baseline CD4 count of 139 cell/mm³ (range 4-842cell/mm³). Hypertension was present in 37 patients (42%), Diabetes in 11 (12%), Tuberculosis in 28 (32%) and HIV-related malignancies in 5 (5%). The median baseline serum creatinine in this group was 298 $\mu\text{mol/l}$ (range 49-3294 $\mu\text{mol/l}$) and the median baseline eGFR was 20.8ml/min/1.73m² (range 1.7-167.6ml/min/1.73m²). The median serum creatinine at 12 months decreased to 162 $\mu\text{mol/l}$ (range 51-1566 $\mu\text{mol/l}$; $p < 0.05$) and 137 $\mu\text{mol/l}$ at 24 months (range 50-1914 $\mu\text{mol/l}$; $p < 0.05$). The median eGFR at 12 months increased to 52.4 ml/min/1.73m² (range 3-

203.9ml/min/1.73m²; p<0.05) and 57.7ml/min/1.73m² (range 2.2-167ml/min/1.73m²; p<0.05) at 24 months respectively. The 3 and 6 month measurement differences were not statistically significant. Median baseline proteinuria was 0.3g/day (range 0.01-1.4g/day). The level of proteinuria at 12 months was 0.11g/day (range 0.01-0.95g/day; p<0.05) and 0.08g/day at 24 months (range 0.02-0.99g/day; p<0.05). Univariate analyses were performed to identify associations between poor renal outcomes and factors including hypertension, diabetes, tuberculosis, malignancy, baseline eGFR, baseline proteinuria level and haemoglobin. Those found to be significantly associated with a poor renal outcome were diabetes (OR 4.9, CI 1.2-18.9) (p 0.02) and baseline eGFR (OR 1.01, CI 1-1.03) (p 0.01). On further multivariate analysis, these predictors continued to be significant: diabetes (OR 4.24, CI 1.02-17.5) (p 0.04) and baseline eGFR (OR 1.01, CI 1-1.02) (p0.017). A total of 13 patients were receiving renal replacement therapy (RRT) prior to ART initiation, 8 haemodialysis and 5 peritoneal dialysis. One patient was initiated on RRT during the study period and eventually went on to receive a kidney transplant in November 2011. 34 patients are still alive during the follow up period (2 year post study dates). 18 patients were known to have died, 3 of these were known to be from renal failure and 1 from complications of Hodgkin's lymphoma. The others passed away at peripheral hospitals or the cause of death was unknown. 35 patients were lost to follow up.

Group 2 The mean age for this group was 41 years, 35 (42%) were female, with a median baseline CD4 count of 298 cell/mm³ (range 2-1217cell/mm³). Hypertension was present in 34 patients (41%), diabetes in 11 (13%), tuberculosis in 25 (30%) and HIV-related malignancies in 2 (2%). The median time from initiation of ART to presentation to the HIV Renal Clinic was 25 months. The median baseline serum creatinine in this group was 172µmol/l (range 54-1723µmol/l) and the median baseline eGFR 38.9ml/min/1.73m² (range 2.7-150.9ml/min/1.73m³). The median serum creatinine at 12 months decreased to 154µmol/l (range 50-2082µmol/l) and 137µmol/l (range 61-1914µmol/l) at 24 months. None of these however, were found to be statistically significant. The median eGFR at 12

months increased to 46.2 ml/min/1.73m² (range 2.9-151.1ml/min/1.73m²) and 47.3ml/min/1.73m² (range 2.5-140.9ml/min/1.73m²) at 24 months respectively. These were also found to be statistically insignificant (p=0.4256). Median baseline proteinuria was 0.3g/day (range 0.01-1.4g/day). The level of proteinuria at 12 months decreased to a median 0.11g/day (range 0.01-0.95g/day) and subsequently increased to 0.21g/day (range 0.02-0.99g/day) at 24 months. The overall change was statistically significant (p=0.0418). All factors analysed for association with a poor renal outcome in the univariate analysis were found to be statistically insignificant in this group. Therefore, further multivariate analysis was not performed. A total of 8 patients were receiving RRT prior to ART initiation, 5 haemodialysis and 3 peritoneal dialysis. 4 patients progressed to ESRD requiring RRT while on ART during the study period. 30 patients are still alive during the follow up period (2 years post study dates). 15 patients were known to have died, 5 of these were known to be from renal failure. The others passed away at peripheral hospitals or the cause of death was unknown. 37 patients were lost to follow up.

A comparison of the two groups in a Kaplan-Meier survival curve in Figure 2 below shows no statistically significant difference in patient survival between group 1 and group 2.

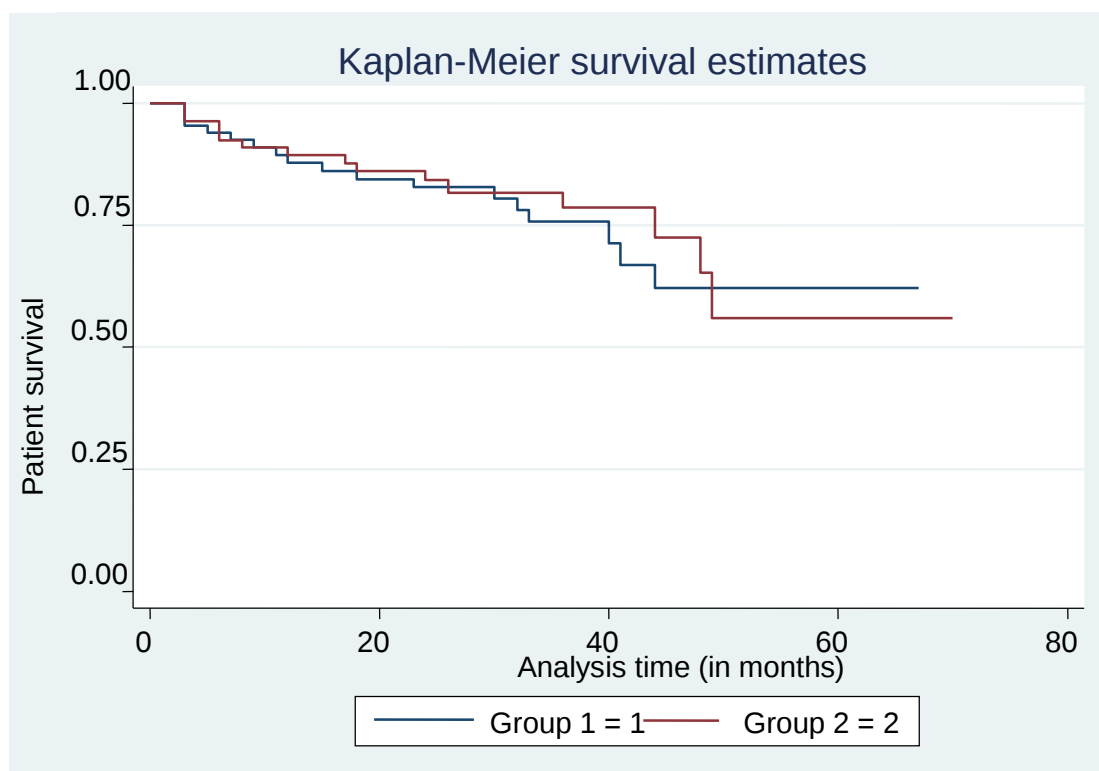


Figure 2 Kaplan-Meier survival estimates plot for overall survival of CKD patients stratified into Group 1 and 2. Analysis of data using the log-rank test showed no difference in survival between the two groups ($p=0.7161$)

4.2 Renal histology

A total of 84 patients had histological information available. 24 patients (20%) (9 in Group 1, 7 in Group 2 and 8 in the excluded group) had HIVAN as a primary diagnosis. 14 (11.6%) patients (8 in Group 1, 3 in Group 2 and 3 in the excluded group) had HIV-ICD. Other histological findings included chronic interstitial nephritis (CIN) (34) (28.4%), acute tubular necrosis (24) (20%), lupus nephritis (3), membranous glomerulopathy (2), membranoproliferative glomerulonephritis (2), IgA nephropathy (1), minimal change disease (1), crescentic glomerulopathy(2) , diabetic nephropathy (3), hypertensive nephrosclerosis (3), thrombotic microangiopathy (2), acute on chronic pyelonephritis (3), ischaemic necrosis secondary to analgesic nephropathy (1) and immunotactoid glomerulopathy

(1). Patients in Group 1 and 2 were then analysed further. It was found that there were no significant differences in factors such as age, gender and CD4 count and so these two groups were combined for analysis.

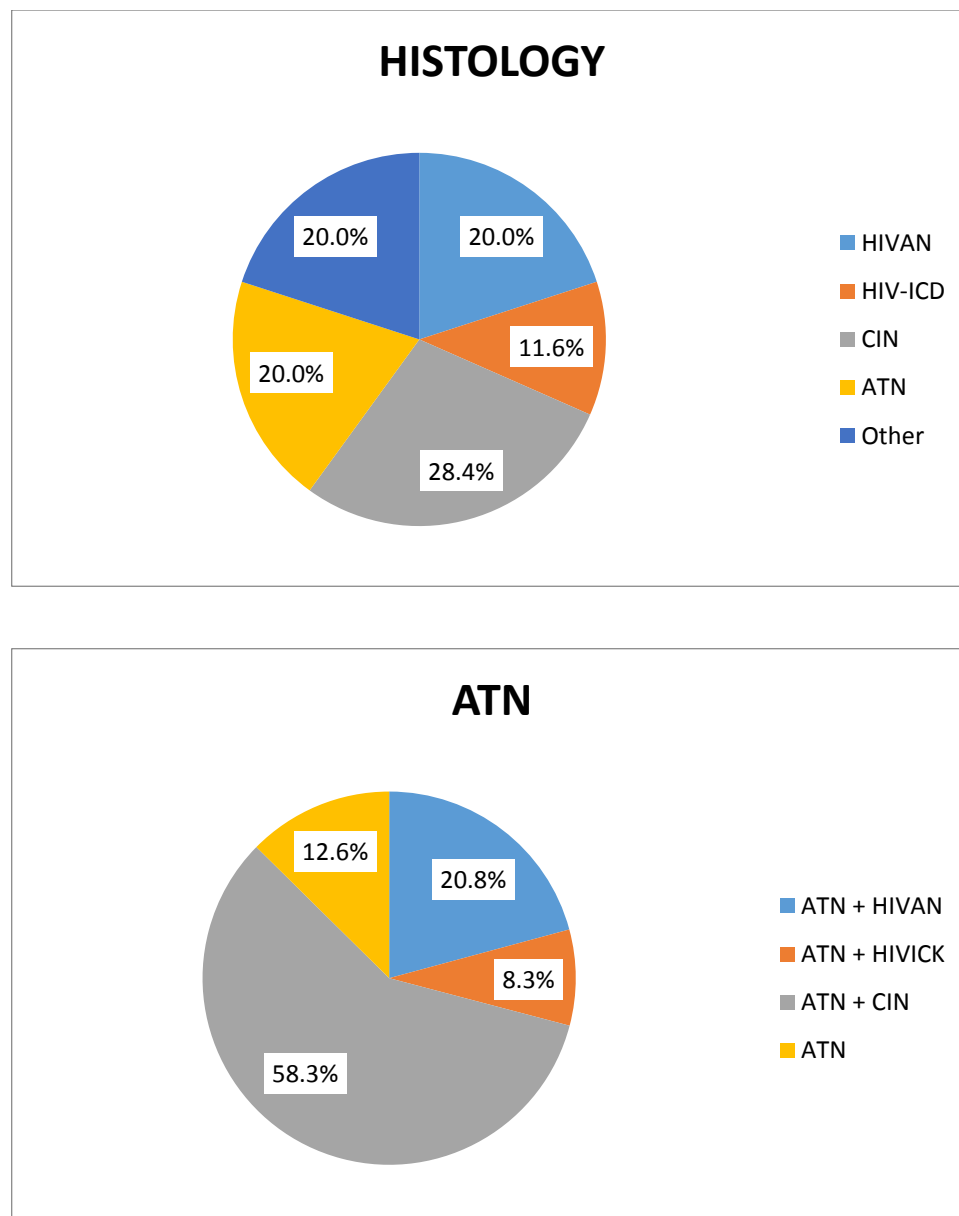


Figure 3 Renal histological patterns in HIV positive patients

HIVAN In this sub group, the changes in eGFR and urine PCR over the 24 month follow up period were found to be statistically insignificant, most likely due to the small sample size. There was however, an increase in the median eGFR from baseline of 26ml/min/1.73m² (range 3.2-117.3ml/min/1.73m²) to 35ml/min/1.73m² (range 5.7-119.6ml/min/1.73m²; p=0.81) at 24 months. A decrease in urine PCR was also observed – 0.45g/day at baseline and 0.11 at 24 months; p=0.48. When the sub group was compared to the entire group (i.e. Group 1+Group2), it was found that there was no statistically significant difference in baseline, 12 or 24 month eGFR or urine PCR values. The histological diagnosis of HIVAN was not associated with a poor renal outcome on univariate analysis (OR 0.72).

HIV-ICD In this group, the changes in eGFR and urine PCR over the 24 month period were also found to be statistically insignificant, most likely due to small sample size. Median eGFR increased from 48ml/min/1.73m² to 92ml/min/1.73m² at 24 months. Median PCR at baseline was 0.45g/day and 0.41g/day at 24 months. There was a significant difference in baseline eGFR in this sub group (48ml/min/1.73m²) compared to the entire group (27ml/min/1.73m²) (p=0.027). There was also a significant difference in eGFR at 12 months. The HIV-ICD group median eGFR was 103ml/min/1.73m² versus the whole study group (Groups 1+2) of 50ml/min/1.73m². There was no significant difference between the urine PCR of this group when compared with the entire group. The histological diagnosis of HIV-ICD was not associated with a poor renal outcome on univariate analysis (OR 0.34).

Other The changes in eGFR and urine PCR over the duration of 24 months were not significant in this group. Median eGFR increased from 37ml/min/1.73m² at baseline to 56ml/min/1.73m² at 24 months. Median PCR at baseline was 0.5g/day, decreasing to 0.13g/day at 24 months. The median eGFR of this group (37ml/min/1.73m²) was higher than that of Group 1 (27ml/min/1.73m²).

However, the differences in eGFR and PCR between the two groups over 24 months were not statistically significant. This histological group was not associated with a poor renal outcome on univariate analysis (OR 0.69).

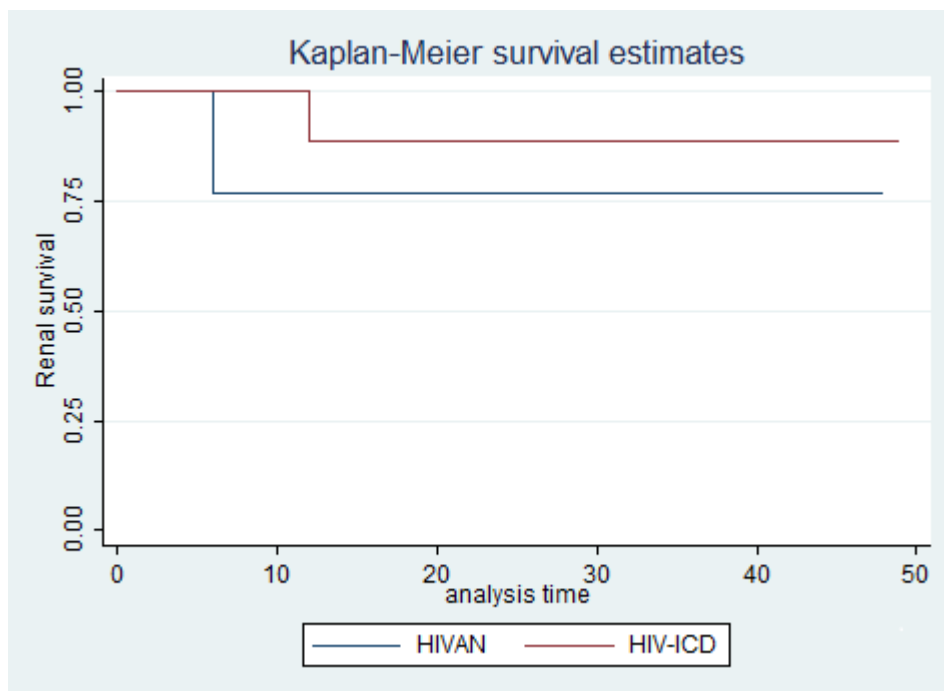


Figure 4 Kaplan-Meier survival estimates for renal survival of CKD patients stratified into two groups according to histology (HIVAN and HIV-ICD). Analysis of the data using the log-rank test showed no difference in survival between the two groups ($p=0.761$)

A comparison of the two groups in a Kaplan-Meier survival curve in Figure 4 above shows no difference in renal survival between HIVAN and HIV-ICD.

5. DISCUSSION

Most patients in Group 1 in this study (i.e. ART-naïve with pre-ART results available) presented with advanced HIV infection (with CD4 counts below 200) and advanced renal disease (CKD stage IV) with a median baseline serum creatinine of 298 μ mol/l (range 49-3294 μ mol/l) and median eGFR of 20.8ml/min/1.73m² (range 1.7-167.6ml/min/1.73m²). There was a significant improvement in patients' renal function by 12 months, which further improved at 24 months. Using the CKD staging system, renal function improved from stage IV to stage III at 12 months and remained stable at 24 months. These findings are consistent with those found in Zambian⁵ and Ugandan⁵⁵ studies, where there was a significant improvement in renal function with the introduction of HAART. This improvement was also reflected in partial or complete resolution of proteinuria which remained stable. Other studies have had similar results with significant resolution of proteinuria with HAART.^{32, 59} Low baseline eGFR was associated with poor renal outcome. This supports the need for early screening for renal disease, with baseline serum creatinine and proteinuria measurement in all HIV positive patients, and early treatment before fibrotic/sclerotic changes are established.^{43, 44} There may also be a need to further evaluate criteria for HAART eligibility. Current WHO guidelines include HIVAN as an AIDS-defining condition, but exclude other causes of renal dysfunction in HIV patients.³⁷ Renal dysfunction as detected by elevated serum creatinine could be looked at as an additional criterion for HAART initiation. Other non-invasive modalities could also be looked at to identify early renal disease. This takes on further significance in resource limited settings where modalities such as histological diagnosis may not be available.

The prevalence of diabetes in our study was 12% and found to be associated with poor renal outcome (odds ratio 4.24, CI 1.02-17.5). These findings are similar to those of other studies such as

the Multicentre AIDS Cohort Study with a prevalence of 14% in HIV infected patients. Concomitant diabetes increases the risk of CKD 10-fold in HIV infected individuals. These findings point to the need for tight glycaemic control and more intensive monitoring in this group of patients in order to prevent the onset of CKD. Of note, concomitant tuberculosis had a relatively high prevalence of 32% but was not associated with poor renal outcome or increased mortality.

Patients in Group 2 (i.e. those on HAART for a median of 25 months when referred to the HIV Renal Clinic with CKD) presented with less advanced renal disease (CKD stage III) and although there was an improvement in renal function, it was not statistically significant and there was no change in stage of CKD. There was a decrease in proteinuria at 12 months, but an increase once again at 24 months. The significance of this change is unknown at this stage. Patients in this group were referred to the HIV Renal Clinic with pre-existing CKD. They may have developed this on HAART, or for many, it may have been missed on initial assessment as it is still fairly common that routine screening for renal disease is not done, even though guidelines recommend routine screening as standard of care.^{33, 43} It is also possible that those with more severe renal dysfunction may have demised prior to presentation to the HIV Renal Clinic. Since Group 2 presented at a median of 25 months after initiation of HAART, if we extrapolate from the results of both groups, it may suggest that renal function initially improves with the introduction of HAART and may stabilize by 12-24 months but will eventually start to deteriorate in the long term. A possible reason for this could be that this group of patients may had a high index of chronic damage (with sclerotic glomeruli and interstitial fibrosis) as they presented to the HIV renal clinic with evidence of persistent renal disease. There have been conflicting reports on this in other studies. Studies found that renal function worsened in patients with HIVAN and a high number of sclerotic glomeruli.^{43, 44} Fabian et al. found that despite a high chronicity index, patients' renal function improved with HAART.³² These findings support early diagnosis of renal disease and initiation of treatment to prevent irreversible renal damage. There

were no factors found to be significantly associated with poor renal outcome in this group of patients.

A study done by Bige et al found that the use of ACE-Is together with ART was associated with better renal outcomes. Our study had too few patients on ACE-Is on follow up for analysis.

The most common histological diagnosis found in the 2 groups was HIVAN, followed by HIV-ICD. These findings are similar to other South African studies.^{10, 11, 14} As has been mentioned before, there have been discrepant reports in studies examining the response of HIVAN to HAART. An American study³⁸ found that there is improvement in renal function with HAART, while another cohort study⁴⁴ reported progression to ESRD with HAART in those whose histology showed a high index of chronic damage. Our study showed an improvement in renal function in HIVAN patients with HAART (although not statistically significant) and was not associated with poor renal outcome on univariate analysis. Patients in the HIV-ICD group had a significantly higher baseline eGFR compared with the entire group, and renal function did in fact improve with the introduction of HAART. There have been discrepancies in studies evaluating patients with histological diagnoses other than HIVAN. An American study¹³ found no improvement in renal function with initiation of HAART while two South African studies^{14, 32} found an improvement in renal function. Of note, the level of proteinuria was similar in HIV-ICD and HIVAN, suggesting that the clinical profile of the two groups may be similar. This supports findings in other studies^{10, 11, 13} that renal biopsy is still the gold standard in differentiating between the different entities in HIV renal disease. Neither histological diagnosis, however, was associated with a poor renal outcome. The third histological group included all other histological diagnoses. There was an improvement in eGFR in this group although it was not statistically significant, probably due to the small sample size. Of note, the largest proportion was

CIN with 41%. A South African study found that there was no resolution of the histological abnormalities in CIN with ARTs³².

6. STUDY LIMITATIONS

There were a number of limitations in the study. Firstly, due to the retrospective nature of the study, some information (including kidney size to confirm CKD) and laboratory data were not available and patients were lost to follow up. Secondly, the MDRD formula was used, which may have overestimated the eGFR in our patients due to the generally lower muscle mass in this group of patients. The small numbers within the histological groups was another limitation and larger studies will be needed to confirm the results of this study. In addition, due to the relatively small number of patients on ACE-Is their impact on proteinuria and renal function could not be assessed.

7. CONCLUSION

Our findings demonstrate that HIV patients with CKD respond well to HAART. This is reflected in improvement in eGFR and improvement in the level of proteinuria. Baseline low eGFR was associated with a poor renal outcome suggesting that initiation of HAART earlier in the course of the disease, before severe renal dysfunction has developed, improves renal outcomes and reduces the burden of HIV CKD. Patients who presented with persistent renal disease despite HAART were less likely to recover renal function, which also suggests implementing the recommendations for earlier diagnosis and treatment of renal disease in HIV patients.

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