Renal dysfunction in HIV positive patients on Highly Active Antiretroviral Therapy (HAART)

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ABSTRACT

TITLE: Renal dysfunction in HIV positive patients on highly active antiretroviral therapy (HAART).

BACKGROUND: The use of HAART has turned HIV/AIDS into a chronic disease and people live longer. They now present with complications related to the treatment, ageing process and the virus itself. Renal dysfunction is a recognized complication in HIV infected patients on HAART and can present as acute kidney injury or chronic kidney disease.

METHODS: A cross sectional study was conducted at Parirenyatwa Hospital on patients receiving HAART. Inclusion criteria were age ≥ 18 years and provision of an informed consent. Clinical data was recorded. Body mass index, CD4 count, serum creatinine, urine for dipstick proteinuria and protein: creatinine ratio was collected. Creatinine was calculated using the Cockcroft-Gault formula. Renal dysfunction was defined as Creatinine clearance (CrCl)< 60mL/min.

RESULTS: A total of 122 patients with complete data were analysed. 69% were females. Mean age of patients was 37.7 ±11.3 years and Body mass index was26.0 ±5.2 kg/m². Renal dysfunction defined as CrCl< 60mL/min was found in 18.9 %,(n =23/122). Microalbuminuria was found to be a risk factor for renal dysfunction [OR 4.24 95% CI 1.00-17.04] $p < 0.049$.

CONCLUSION: Renal dysfunction is common among patients on HAART and micro albuminuria is a risk factor for developing renal dysfunction. For patients on HAART routine urine protein: creatinine ratio and calculation of creatinine clearance should be done at regular intervals to monitor if the patients are developing renal dysfunction.

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CONTENTS

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AKI	Acute kidney injury
ART	Antiretroviral therapy
BMI	Body Mass Index
CD4	Cluster of differentiation 4
CI	Confidence Interval
CKD	Chronic Kidney Disease
CrCl	Creatinine clearance
DART	Development of Antiretroviral Therapy in Africa Trial
EFV	Efavirenz
eGFR	estimated Glomerular filtration rate
ESRD	End Stage Renal Disease
GFR	Glomerular filtration rate
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy

HOAT	Human Organic Anion Transporters
IQ	Interquartile range
MDRD	Modification of Diet in Renal Disease
MRP	Multidrug Resistance Proteins
OPD	Outpatient department
OR	Odds ratio
SD	Standard deviation
TDF	Tenofovir

1. INTRODUCTION

The advances in development of Highly active antiretroviral therapy (HAART) have turned HIV/AIDS into a chronic disease and people are living longer.[1] Individuals are now presenting with complications related to the treatment , the ageing process and as well as the infection per se .[2] These complications might be related to heart, lung, hepatic or renal disease which could be associated with higher mortality.[2] Africa endures greater than 60% of the global burden of HIV, however, data on renal disease is limited to developed countries with very few studies done in developing countries.[3-4] Kidney function has been estimated to be abnormal in up to 30% of HIV infected patients.[5]The few outpatient renal screening studies from Africa describe varying prevalence from as low 6% to a high of 50%.[6] This can be explained by different criteria used in defining kidney dysfunction, study design used and subject population studied.

Renal dysfunction may present as acute kidney injury (AKI) or chronic kidney disease (CKD).[7]Traditional risk factors such asdiabetes mellitus and hypertension are the same for both HIV infected patients and HIV negative patients to develop renal dysfunction.[5] However, in HIV positive patients other risk factors like older age, low nadir CD4 counts and cumulative exposure to antiretroviral therapy (ART) agents are associated with kidney disease.[8]In hospitalised patients sepsis and volume depleting conditions like gastroenteritis are the leading causes of renal dysfunction.[9-10]

Different ART agents are also a risk factor for renal dysfunction.[9]The nucleotide analogue tenofovir-(TDF) has become a prominent component of combinations of ART due to its tolerability, convenient dosing and potency when used with two other active ART agents.[11]

However, concerns regarding its renal toxicity remains. Several case reports and cohort studies have noted varying degrees of TDF associated renal tubular dysfunction or small declines in estimated glomerular filtration rate (eGFR).[12-13] However, the reported prevalence of renal dysfunction is very low being about 2% in observational cohort studies in which patients on tenofovir have been followed up.[13]The lower prevalence in these studies than what might have been expected could be due to varying surveillance standards in different studies; in addition outside the controlled environments of clinical trials, patient populations are different, treatment is more complex and clinical trials protocol might be difficult to apply. Overall there have been significant benefits of HAART with overall decline in rates of renal failure and end stage renal disease (ESRD).[14-15] A large European cohort study which followed up patients admitted in acute care hospitals in New York State during 1995 (pre ART) and 2003(post HAART) showed that the incidence of acute renal failure declined in patients admitted during 2003. In 1995 the odds ratio (OR) was, 4.62; 95% confidence interval (CI), 4.30-4.95 and in 2003 OR, 2.82; 95% CI, 2.66- 2.99.[16] In the post HAART cohort acute renal failure was associated with traditional risk factors such as age, diabetes mellitus, chronic kidney disease as well as acute or chronic liver disease. However, this study was conducted in a mainly Caucasian study population and it might not be feasible to generalise the results to patients in our setting. Studies done in developed countries have shown that male gender and black race are more prone to renal impairment compared to other races.[29] This has been attributed to late presentation, poor socioeconomic status and an increased risk of HIV infection.

Currently over 25 million people in Africa have been diagnosed as having HIV/AIDS and can be expected to receive Antiretroviral therapy (ART) at some point in the course of the

disease and many patients will be on ART for life.[5] As life expectancy continues to improve with more potent therapies, it remains critical to identify persons with early and mild to moderate renal dysfunction in order to provide the greatest opportunity to modify risk of progression to CKD. A low GFR < 60mL/min meets criteria for CKD. Epidemiological data links low GFR to an increased frequency of hospitalisation, cardiovascular events and death.[29]

Treatment guidelines have been developed for the screening and management of CKD in HIV infected patients.[8] Recommendations include routine urinalysis for proteinuria and calculated creatinine clearance or eGFR, as well as careful attention to comorbidities like hypertension and diabetes mellitus that may contribute to poor outcomes in kidney disease.[8]Tenofovir has become part of our first line treatment because of its convenience in dosing. In the presence of significant renal dysfunction dose adjustments of TDF should be done or an alternative drug used.[17]

2. LITERATURE REVIEW

2.1 RENAL DYSFUNCTION IN DEVELOPED COUNTRIES

Early in the epidemic of HIV most patients were diagnosed as having HIV associated nephropathy (HIVAN), an aggressive form of collapsing focal segmental glomerulosclerosis caused by direct HIV infection of the kidney in genetically susceptible patients.[12] Blacks are more predisposed to the disease and it had been found that the MYH9 associated gene is involved in the development of idiopathic HIV 1 related focal segmental glomerulosclerosis in people of African descent. It is characterised by nephrotic range proteinuria, renal failure and large echogenic kidneys on ultrasonography.[12, 18]Pre-HAART HIVAN was associated with rapid progression to ESRD and death. With the widespread use of HAART HIVAN prevalence has decreased markedly.[19]

During the pre –ART era, renal failure was associated with younger age, advanced immunosuppression, volume depleting conditions and septicaemia.[16] A hospital based study, done in New York, United States of Americaby Wyatt et al compared the incidence of Acute renal failure(ARF)in HIV positive individuals in 1995 (pre ART era) and 2003 (post HAART era). The results showed that HIV infected patients had an increased incidence of acute kidney injury in the pre HAART era compared to post HAART era.[16]It was an observational study retrieving information from a database and the diagnosis of acute kidney injury was based on clinical judgement and documentation by the treating physician. This could have introduced bias and the results might have been a false representation of the population studied. There was also no laboratory data documented furthermore raising questions about the definition of renal dysfunction that was used. They might have underestimated the burden of renal failure because of lack of laboratory values and also inaccurate judgement by the treating physician.

In a cross sectional study done at Washington University Outpatient Infectious Disease Clinic in America, 845 patients were recruited (63, 7% males, 36, 3% females).[20] Overton et al found out that 35, 4%of patients who were HIV infected had mild to moderate renal dysfunction defined as eGFR< 90mL/min and proteinuria, 5.3% of participants had CKD defined as eGFR<60ml/min. In this study Overton and colleagues found that tenofovir and stavudinewere significantly associated with declining in renal function. HAART generally consisted of three or more antiretroviral drug combinations and cumulative exposure to ART drugs might have caused the decline in renal function.[20]However, TDF was not a significant predictor of lower GFR in multivariate analysis.

Franceschini and colleagues looked for incidence of acute renal failure among ambulatory HIV infected patients; they obtained data from the Department of Veterans Affairs HIV Clinical Case Registry in America. It was an observational cohort study. They recruited 754 patients between 2000-2002 ; about ten percent of patients experienced at least one episode of ARF during the two year period.[9] Acute renal failure occurred more often in men, hepatitis C co-infected patients, those with low CD4 counts, and high RNA levels, and a prior history of an AIDS defining clinical condition. Race was not associated with increased incidence of ARF in contrast to other studies that have shown an increased prevalence of CKD in black populations. Drugs caused about a third of all ARF. Indinavir, tenofovir and nevirapine were the only ART drugs shown to have an association with ARF.[9]

The Manhattan HIV Brain Bank established in Americawas a prospective cohort of antiretroviral experienced patients and looked at histology specimens from those individuals who had consented to post mortem organ donation.[21] Of the 89 kidney tissue donors, 27 had chronic renal disease based on the presence of proteinuria and an eGFR less

than 60ml/min/1,73m^2 for at least 3 months. Most common diagnoses were arterionephrosclerosis, HIVAN and glomerulonephritis. The prevalence of chronic renal disease was common among black female population.[21] However, there was no association between chronic renal diseases or renal pathology and HIV related factors such as HIV viral load and CD4 counts. This contrasted with other studies that had shown that overt renal disease tends to be associated with low CD4 counts.

In a cross sectional study done in Brazil the prevalence of chronic renal disease diagnosed on the basis of proteinuria and eGFR less than or equal to 60ml/min/1.73m^2 was 8.4%.[15] The risk factors were hypertension, time on HAART and tenofovir exposure. They postulated that prolonged use of HAART could be associated with greater long term renal toxicity as there was a 15% increase in the prevalence of chronic kidney disease per year of additional exposure to HAART. However, this was a cross sectional study hence it might have included patients with reversible causes of renal dysfunction contributing to the high prevalence that was found.

In a prospective study to find an association between renal disease and outcomes among HIV infected women receiving or not receiving antiretroviral therapy, done in the United States of America, Szczech LA et al, found that proteinuria and / or an elevated creatinine level are associated with an increased risk of death among women before the widespread use of HAART and after initiation of antiretroviral therapy.[22]The study was done before and after the widespread of HAART and it was shown high creatinine levels and presence of proteinuria increased risk of getting AIDS defining illness. Proteinuria has been demonstrated to be associated with more-advanced HIV infection manifested by a lower CD4 lymphocyte count and a higher HIV RNA level. The mechanisms for this association are

unclear. Proteinuria may be a marker for diseases, such as HIVAN, that are associated with a reservoir of viral replication in the kidney and resultant systemic implications. Immune dysfunction associated with worsening renal disease could contribute to the risk of AIDS defining illness among HIV-infected women with higher creatinine levels.

2.2 RENAL DYSFUNCTION IN AFRICA

More than two thirds of the world's HIV infected individuals live in Africa but very few studies have been done to find the prevalence of renal dysfunction in patients on HAART. In those few studies done, the prevalence is variable, thought to reflect a genetic heterogeneity across Africa as well as variability in access to care and different estimates of GFR used during the studies.

In Zambia, Mulenga et al found a prevalence of 33.4% renal insufficiency at initiation of HAART with increased mortality among those patients with more severe renal insufficiency within 90days and also two year survival analysis after initiating HAART.[23] Renal dysfunction was characterised using the Cockcroft-Gault method with about 3.1% having severe renal dysfunction defined by a creatinine clearance of less than 30mL/min.[23] In this study they did not do routine urinalysis; this might have missed some patients who present with proteinuria but with preserved creatinine clearance. Emem et al in a cross sectional study from Nigeria, found a prevalence of 38% renal dysfunction determined by at least 1+ dipstick albuminuria and/or raised serum creatinine concentration (greater than 132micromoles/l) in 400 HIV-AIDS patients.[24] They attributed the high prevalence to late presentation as evidenced by low CD4 counts in the affected patients.

In Uganda, Peters et al evaluated the importance of monitoring renal function in a rural population of patients on HAART.[25] They recruited 508 HIV positive patients with

symptomatic disease or CD4 counts less than 250cells/ml. Patients with an initial eGFR of less than 25ml/min were excluded. They monitored patients for two years and these patients were on HAART comprising ofstavudine, lamuvidine, nevirapine or efavirenz. Results showed that 8% had an elevated serum creatinine at baseline greater than 233micromol/l. Of the 508 patients, 20% had a reduced baseline renal function with creatinine clearance of 25-50ml/min. There was a 16% decline in the median creatinine level during follow up, and the median creatinine clearance rose by 21% after 24 months of follow up. More marked improvements were noted among patients with more depressed renal function at baseline.[25]From this study it was noted that HAART resulted in the improvement of renal function. However, about 5% of the study population had a significant decline in renal function despite achieving viral load suppression. This decline was attributed to renal disease that does not improve with HAART for example renal lesions other than HIVAN like immune complex glomerulonephritis, membranous nephropathy or diabetic nephropathy.[25]

Another comparative cross sectional study was done in Ethiopia by Kahsuand colleagues at a referral hospital.[26]They recruited 307 HIV positive patients, 153 HAART naïve and 154 on HAART. The prevalence of renal impairment based on GFR calculated using the Cockcroft-Gault method in HAART naïve was 30, 1% and the prevalence of renal impairment in those on HAART was12, 9%. Overall proteinuria in the study was 17.9%.[26]The prevalence of renal impairment was lower in those on HAART and this might be due to improved immune status and also improvement in weight as this was incorporated in calculating eGFR. For the patients not yet on HAART it was shown that proteinuria and low CD4 counts had significant association with the prevalence of renal impairment.

The DART trial conducted in Uganda and Zimbabwe, had an observational analysis within a randomised trial of ART management strategies.[27]The trial included 3316 participants with CD4 count less than 200cells/ml and creatinine levels less than 360umol/l at baseline. Renal function was monitored for up to 96 weeks while patients were on different ART regimens. Mild renal impairment was seen in 45% of patients based on eGFR 60-90ml/min at baseline. Patients with more severe decrease in GFR at baseline showed a greater increase over 96 weeks of follow up. Severe reductions in GFR were seen in 52 patients during the period with no relation to ART agents. The conclusion was that renal impairment was highly prevalent among patients with a low CD4 count and this tended to improve with ART.[27] However, the results cannot be generalised as patients with high creatinine (>360 micromoles) were excluded from the study.

In Zimbabwe, Fana et al conducted an outpatient study for HIV patients who were antiretroviral naïve and found that 7.5% of the participants had renal dysfunction described as creatinine clearance less than 60ml/min. Proteinuria was found in 45.9% of the participants. Risk factors for renal dysfunction were age, low body mass index and proteinuria.[28] The results of the study need to be taken in the light that it was a cross sectional study with a point estimate of a patients renal function and it might have included patients with reversible causes of renal failure. Ideally the definition of chronic kidney disease require the abnormalities to be there at least for 3 months hence in this study it might have included patients with acute kidney disease.

2.3 RISK FACTORS OF RENAL DYSFUNCTION AMONG HIV INFECTED PATIENTS

Various risk factors predispose HIV infected patients to developing renal dysfunction. Volume depleting conditions are a major cause of prerenal failure in HIV patients with diarrhoeal illness and vomiting from any cause being the main cause of renal

dysfunction.[16]Franceschini and colleagues showed that ARF remains an important complication of HIV in patients on HAART.[9] ARF most often resulted from pre renal causes or acute tubular necrosis and was associated with advanced HIV infection CD4 < 200cells/ml, HIV RNA copies > 10000ml,any HAART use and Hepatitis C co infection. More than half of ARF cases were due to underlying infections76% of which were AIDS defining illnesses and almost 3% of them necessitated hospitalisations. Drug related complications accounted for nearly a third of cases and amphotericin B was the most common drug causing nephrotoxicity.[9]

Race is an important risk factor for CKD with 30% of patients with CKD comprising black people who have ESRD according to United States of America renal data system. Young black males with HIV infection have an 11 fold increased risk of CKD compared to their white counterparts.[29] The reason for this is not well understood but it may be due to greater risk of diabetes and hypertension, lower socioeconomic status and poorer access to health care. HIV increases the risk of renal dysfunction and patients with other comorbidities are also at an increased risk of renal dysfunction.

Due to the use of HAART people are now living longer and there is an increased risk of CKD as GFR also decreases with age. In the HAART era traditional risk factors of hypertension, diabetes and ageing are more prevalent as people will be living longer and some ART medication causes dyslipidaemias. In developed countries Hepatitis C virus (HCV) co-infection has been associated with increased risk of acute kidney injury and is an important cause of mortality and morbidity in patients with HIV.[30] In Sub-Saharan Africa hepatitis B has greater significance than hepatitis C in patients who are HIV infected. In a subgroup study done in the DART trial in Zimbabwe a high level of exposure to hepatitis B was observed as

evidenced by 55.4% anti-HBC sero-prevalence.[31]This might be attributed to the fact that HIV and hepatitis B are both sexually transmitted. A study by Lopes et al demonstrated a multifactorial cause of renal dysfunction with sepsis being the most prevalent risk factor of developing acute renal failure. This was a cohort study489 hospitalized HIV-infected patients to analyze the incidence, etiology and risk factors of AKI, as well as its impact on in-hospital mortality. They found that 18% of patients developed AKI within the hospitalization. AKI was multifactorial in approximately one-half of cases, and the most common etiologies were sepsis, nephrotoxic drug administration, volume depletion and radiocontrast use. Preexisting hypertension, AIDS, sepsis and nephrotoxic drug administration were associated with increased risk of AKI. The development of AKI was associated with lengthened time of hospitalization and increased in-hospital mortality of those patients. Furthermore, there was a relationship between more severe AKI and increased in-hospital mortality.[32] Malnutrition, age and severity of HIV disease measured by using CD4 counts measurements were common risk factors in hospitalised HIV with kidney dysfunction in a Nigerian study.[24]

2.4 IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON RENAL FUNCTION

Renal impairment secondary to HAART can present in different forms as acute kidney injury, acute tubular necrosis, kidney stones and CKD. Dose adjustments of HAART are recommended for patients with renal impairment.[33]The most common drugs causing renal dysfunction are indinavir and tenofovir but isolated cases of other drugs have been reported.[8] The following table shows some of the ART drugs which are nephrotoxic and risk factors associated with them.[29]

Table 1 Antiretroviral shown to be potentially nephrotoxic.

Drug	Reported Nephrotoxicity	Risk Factor
Abacavir	*Acute renal failure, interstitial Nephritis (rare)*	
Atazanavir	*Case report nephrolithiasis, interstitial nephritis, reversible renal failure*	
Didanosine	*Tubular dysfunction (rare)*	
Efavirenz	*Single report of hypersensitivity reaction*	
Enfurvitide	*Single report of glomerulonephritis*	
Indinavir	*Crystalluria, nephrolithiasis, dysuria, papillary necrosis, acute renal failure*	*Concomitant treatment with low dose ritonavir,-urine pH . 6, low lean body mass, treatment with trimethoprim-sulfamethoxazole, acyclovir*
Lamivudine	*Tubular dysfunction (rare)*	
Ritonavir	*Reversible renal failure, but nephrotoxicity not definitely defined*	*Concomitant treatment with nephrotoxic drugs, underlying renal pathology*
Stavudine	*Tubular dysfunction (rare)*	
Tenofovir	*Tubular dysfunction, Fanconi (rare), decreased glomerular filtration rate,*	*Low body weight, impaired baseline renal function, concomitant treatment with potentially nephrotoxic agents*

2.4.1 PROTEASE INHIBITORS (PI)

Indinavir is a protease inhibitor that can cause nephrolithiasis, crystalluria, dysuria, papillary necrosis and acute renal failure. The drug is no longer used in Zimbabwe. A 1997 study showed urinary crystals secondary to indinavir in 20% of all patients who used it and 3% progressed to nephrolithiasis.[34] A study of 1259 patients estimated that the incidence of urological complications was 8.3% cases per 100 treatment years. Prevention of indinavir nephrotoxic effects was by adequate hydration, drinking greater than 1500mls of fluids per day.[35]

Case reports of renal colic and nephrolithiasis in patients taking lopinavir and ritonavir and atazanavir have been reported. Atazanavir has a good safety profile and is taken once daily. The drug is used as second line in Zimbabwe.[36] Dose related hyperbilirubinemia is a very

common adverse effect of atazanavir, because of the competitive inhibition of the enzymatic uridine diphosphate glucuronosyl transferase pathway of bilirubin glucuronidation. Crystallization in urine has not been previously reported although renal colic is mentioned as rare adverse events. Up to 7% of atazanavir is excreted unchanged in urine. The solubility of atazanavir is increased in acidic fluids. Urolithiasis can occur in patients on ritonavir boosted atazanavir.[37,38] A retrospective study of HIV patients from France found 11 cases of nephrolithiasis among 1 134 patients receiving atazanavir. Infrared spectrophotometry confirmed the presence of atazanavir urinary stones in each case.[39]

2.4.2 NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

Tenofovir has structural similarity to adefovir and cidofovir which are known to cause renal impairment. Tenofovir renal impairment can present as acute tubular necrosis, decreased GFR or reversible tubular dysfunction for example Fanconi syndrome.[10]Fanconisyndrome consists of a generalised defect of membrane transporters in the proximal tubule leading to renal loss of glucose (with normal serum glucose), loss of phosphorus, calcium, uric acid, amino acids, bicarbonate and tubular proteins causing renal tubular acidosis type II. Most case reports do not have the whole spectrum of Fanconi syndrome but they might be just an elevation of serum creatinine, with hypophosphaturia and glycosuria.[10, 12]

The way tenofovir induces renal toxicity remains unclear. There are specific Human Organic Anion Transporters (hoat1 and hoat3) in combination with Multidrug resistance Proteins (MRP2/MRP4) in the proximal renal tubule that secrete tenofovir in the urine. It has been hypothesized that when ritonavir is given in combination with tenofovir , ritonavir causes an inhibition of MRP2 , and therefore causing a decrease in the efflux of tenofovir leading to toxic increase of intracellular tenofovir concentration.[40] However, large clinical trials in treatment naïve patients (normal renal function baseline) have not reported a negative

impact of tenofovir on renal function. Risk factors for getting tenofovir nephropathy include low body mass index, impaired renal function at baseline and co administration with other nephrotoxic drugs.[40]

In the HIV Outpatient study when 595 patients on tenofovir were compared to 521 patients not on tenofovir, tenofovir was associated with a statistically significant decrease in GFR but only 1.1% of patients on tenofovir discontinued treatment.[41] In the DART trial 2469 (74%) of the 3316 enrolled patients were on tenofovir / zidovidine and lamuvidine.[27] The overall incidence of severe reduction in GFR was low 1.6% and no difference in renal safety endpoints was detected between the regimens. Most data show low rates of discontinuation of drug due to renal dysfunction (0-2%) when tenofovir is used.

GFR can decrease 7-10mL/min over the course of one year in tenofovir patients but in most studies the increase in serum creatinine level was too small to be clinically significant. Long term decrease in GFR over long periods of time have not been reported but if this was to happen this will cause serious consequences hence the importance of monitoring renal function in patients on tenofovir. For those with impaired renal function at baseline (GFR <60mL/min) it would be wise to find alternative treatment.

2.4.3 OTHER ART DRUGS

Nucleoside reverse transcriptase inhibitors have generally a good renal profile. Case reports of didanosine, stavudine and lamuvidine have been reported associated with tubular dysfunction. One case report of abacavir acute renal failure and biopsy proven interstitial nephritis has been reported.[38]

2.5 Rationale

The advance of HAART has turned HIV/AIDS into a chronic disease. Patients are now presenting not with complications of the disease itself but with complications of having increased life expectancy and also complications of the HAART therapies. They are more prone to complications of heart, lung and kidney disease. Renal insufficiency has been shown to be an independent risk factor for mortality among HIV infected patients. Unfortunately little is known about its prevalence in those patients on HAART in Africa. Most studies were done at ART initiation, and on patients with severe HIV disease. Late presentations and under reporting are some of the factors that limit data in developing countries. Identification of asymptomatic patients will aid in early management of patients and adjustment of doses of certain HAART therapies.

3. MEASURES OF RENAL FUNCTION

3.1 Definitions and staging of chronic kidney disease

3.1.1 Acute kidney injury (AKI)

Acute kidney injury is a clinical syndrome characterised by rapid decrease in renal excretory function with accumulation of products of nitrogen metabolism and failure to maintain fluid electrolyte and acid base homeostasis. The Acute Dialysis Quality Initiative (ADQI) was formed and represents the efforts of a working group seeking to develop an evidence based definition of AKI.[42]Theycame up with the RIFLE criteria. RIFLE defines three grades of severity of AKI: Risk, Injury, Failure(RIF) on the basis of graded changes in serum creatinine or urine output. It has two outcome variables Loss and End stage kidney disease (LE) based on the duration of loss of kidney function.[43]In 2005 the Acute Kidney Injury Network (AKIN) endorsed the concept of RIFLE with minor modifications. The new terminology enables healthcare professionals to consider the disease as a spectrum of injury. It extends from less severe forms of injury to more advanced that may need renal replacement therapy. It has been used in over 100,000 studies in nephrology and critical care; however it may have weaknesses.

The RIFLE criteria categories are defined according to the estimated GFR and urine output:[44]**R**isk of renal dysfunction is defined as 1.5 fold increase in serum creatinine or GFR decrease >25% or urine output less than 0.5ml/kg/hr for 6 hours.

Injury to the kidney is defined as two fold increase in serum creatinine or GFR decreases by >50% or urine output <0.5ml/kg/h for 12 hours.

Failure of kidney function is defined as threefold increase in serum creatinine or GFR decreases by >75% or serum creatinine greater than or equal to 4mg/dL or acute rise in

serum creatinine greater or equal to 0.5mg/dL or urine output <0.3ml/kg/h for 24hours or anuria for 12hours.

Loss of kidney function defined as complete loss of kidney function greater than 4 weeks.

ESRD – end stage kidney disease which persists for >3 months.

3.1.2 Chronic kidney disease (CKD)

According to the National Kidney Foundation, CKD is evidence of kidney damage that persists for greater than three months.[8]A useful indicator of kidney damage is elevated urinary protein excretion measured qualitatively with a urine dipstick or quantitatively with a spot urine protein to creatinine ratio. Microalbuminuria refers to elevated excretion of albumin above normal ranges but below the level of detection by dipstick test for protein. Persistent proteinuria is the principal marker of kidney damage.[44] Severity of damage is graded according to renal function on the basis of GFR or creatinine clearance into five stages.

CKD stage 1 is kidney damage with normal or increased GFR above 90ml/min/1.73m^2.

CKD stage 2 is kidney damage with mild or reduced GFR ranging 60-89ml/min/1.73m^2.

CKD stage 3 is kidney damage with moderate GFR ranging 30-59ml/min/1.73m^2.

CKD stage 4 is kidney damage with severe GFR ranging 15-29ml/min/1.73m^2.

CKD stage 5 is ESKD with GFR below 15ml/min/1.73m^2 and in need of permanent renal replacement therapy in form of dialysis[8].

A GFR < 60 meets criteria for CKD, a cut off supported by epidemiological data linking low GFR to an increased frequency of hospitalisations, cardiovascular events and death.[45]

3.1.3 Estimation of GFR and assessment of proteinuria

The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations provide useful estimates of GFR in adults.[46,47]The use of serum creatinine concentration is no longer recommended as the sole means of measuring renal function. Neither of these tests has been validated in patients with HIV infection and renal disease and in African patients. MDRD was derived from patients with low GFR and therefore can yield variable results in people with normal renal function. In spite of this they remain the mostly highly validated formulas available and both equations are more sensitive than measuring serum creatinine alone. In the DART study MDRD equation overestimates GFR, 103 vs 89ml/min/1.73m^2 compared to the Cockcroft Gault method showing that the two formulas can give different results.[27]In this study the Cockcroft-Gault formula will be used to estimate GFR

Assessment of proteinuria is recommended in renal disease. The ratio protein or albumin to creatinine in untimed urine specimen has replaced measurement of protein excretion in 24 hour urine collection.[44]Theratios decrease the errors associated with 24 hour urine collection. It also corrects for variation in urine protein concentrations due to hydration status. Early detection of kidney disease associated with proteinuria allows early intervention to retard progression. Proteinuria measured by a urinary dipstick and urinary protein: creatinine ratio will be used as a marker of kidney damage.

4. Research question

What is the prevalence of renal dysfunction in HIV infected patients on HAART at a tertiary care institution in Zimbabwe?

5. OBJECTIVES

5.1 General Objective

To determine the prevalence of renal dysfunction in patients on HAARTwho are being followed up at the Parirenyatwa Hospital, Family Care Centre

5.2 Specific objectives

5.2.1 Primary objective

To determine the proportion of HIV infected patients on HAART for equal or greater than three months who have renal dysfunction [Renal dysfunction defined as creatinine clearance less than 60mls/min calculated by the Cockcroft –Gault formula]

5.2.2 Secondary objective

To identify factors associated with renal dysfunction in HIV infected patients on HAART

6. STUDY HYPOTHESIS

6.1 Alternative hypothesis

The prevalence of renal dysfunction in HIV infected patients on HAART at a tertiary care institution is less than 7, 5% [based on a cross sectional study done on HAART naïve patients in Zimbabwe.[28]]

7. RESEARCH METHODS

7.1 Target population

HIV positive patients on HAART aged more than 18 years being seen at The Family Care Centre (FCC), an HIV clinic at Parirenyatwa Hospital, a tertiary care centre in Zimbabwe

7.2 Study design

Cross sectional study

7.3 Recruitment

Patients who were attending the HIV clinic at The Family Care Centre at Parirenyatwa Group of Hospitals and aged 18 years and above were invited to enrol in the study. Those who consented were recruited into the study. The patients recruited were those coming either for routine drugs pick-ups, for bleeding for viral loads or for a scheduled review by a doctor. The participants were recruited over a five month period November 2014- March 2015. The desired number of 118 was achieved and total recruited was 124 participants.

7.3.1 Inclusion criteria

- Patients coming for review at an HIV clinic in Harare, Zimbabwe
- HIV positive patients on HAART for greater than or equal 3 months
- Age equal or greater than 18 years
- Written informed consent

7.3.2 Exclusion Criteria

- Patients with past history of renal disease
- Pregnant patients
- History of hospitalisation in the preceding 1 month

7.4 Study Factors

7.4.1 Primary study factor

Renal function in patients on HAART measured using the Cockcroft –Gault method

7.4.2 Secondary factors

1. Demographics; Age (*years),* Sex (*male/female),* Marital status (*married /divorced/single)*

2. Clinical history; Family history of renal disease, History of opportunistic infections, Current and previous medications used, ART history and adherence

3. Clinical measurements; Weight *(Kg),* Height *(m),* Body mass index (*Kg/m^2*), Blood pressure *(mm/Hg)*

4. Laboratory measurements; Current Serum creatinine (*µmol/L),* Estimated GFR *(ml/min/1.73m^2*), Urine dipstick *(protein positive/haematuria positive/ leucocytes positive),* Urine protein : creatinine ratio *(mg/mg),* Random blood glucose *(mmol/L),* *Current* CD4 counts *(cells/$mm^{3)}$*

7.5 Outcome factors

7.5.1 Primary outcome

The proportion of participants with renal dysfunction defined as creatinine clearance less than 60mls/min calculated by the Cockcroft –Gault formula

7.5.2 Secondary outcome

- Proportion with proteinuria [urine dipstick proteinuria [>1+]

- Urine protein: creatinine ratio [greater than 0.16]

- Proportion with urine dipstick haematuria [>1+]

7.6 Methods

Patients who were attending the HIV clinic at The Family Care Centre at Parirenyatwa Group of Hospitals and aged 18 years and above were invited to enrol in the study. Those who consented were recruited into the study. The patients recruited were those coming either for routine drug pick-ups, for bleeding for viral loads tests or they had come for a scheduled review by a doctor. The participants were recruited over a five month period November 2014- March 2015. The desired number of 118 was achieved and finally 124 participants were recruited. The increased number of patients being recruited will allow for errors in collecting data or missing data that may be realised when doing statistical analysis. Demographic variables were obtained using a structured data collection sheet, and details of previous illness or current opportunistic infections like tuberculosis or meningitis were taken. Duration of known HIV status and period of being on HAART was documented. Information on ART medications a patient from initiation up to the present day of recruitment was collected. Some patients recalled this information and others provided the information from the standard outpatient card or booklet. This tended to produce recall bias. Participants were asked about current prescriptions or medications taken a month before being recruited particularly if they had been on non-steroidal medication, or potentially nephrotoxic drugs. A clinical examination was conducted; weight in kilograms and height in meters was measured to calculate the body mass index (BMI). Blood pressure measurement was done using a calibrated manual mercury sphygmomanometer. Each participant had two blood pressures taken, one on each arm and blood pressure was only measured once. A glucometer was also done using a Gluco Plus machine and it was one finger prick recorded.

A spot urine sample (approximately 20ml) was collected and examined by a multi test urinary dipstick for proteinuria, haematuria, leukocytes. All dipstick tests were performed within 2 hours of urine collection. Urine was also kept and sent to the University of Zimbabwe laboratory for urine protein: creatinine ratio (mg/mg). This measurement was determined by the Mindray BS 200 machine used by the University of Zimbabwe laboratory. Samples of urea and electrolytes were collected in clot activated tubes and serum creatinine concentration was determined by the Modified Jaffe Method using the Mindray BS 200 machine. Blood for CD4 counts (3ml) was collected in an anticoagulated tube and sent to the laboratory on the same day. The Partec CD4 easy count kit was used to measure the CD4 count. Samples were delivered within four hours of collection hence no special storage was needed for all samples. See appendices for full laboratory data.

7.7 STATISTICAL ANALYSIS

7.7.1 Sample size

The sample size was 107 calculated by Dobson's formula based on confidence interval 95% and a 5% margin of error and an estimated prevalence of renal dysfunction of 7.5% [based on a cross sectional study done on HAART naïve patients in Zimbabwe.] A total number of 118 patients were recruited after an adjustment of 10% to the sample size to cater for spoilt samples that could not be processed

$$n = \frac{Z^2 \times (P) \times (1-P)}{d^2}$$

n=sample size Z=static for a level of confidence

P=expected proportion/prevalence

d=precision

Z=1, 96 for confidence level of 95%

7.7.2 Data management

Data entry was in Epi info version 7. Means and standard deviation were generated for variables that were normally distributed**.** Median and interquartile ranges were used for asymmetrical data. For categorical data, for example gender, frequencies were used. The study variables were age, sex, marital status, weight and height, clinical data and laboratory measurements**.** Univariate and multivariate analysis were used to determine the association of risk factors and renal dysfunction. Crude odds ratio with corresponding confidence interval and p-values were reported. Evidence of association was considered for p- values <0.05

7.8 Ethical consideration

Ethical approval from Joint Parirenyatwa University of Zimbabwe College of Health Sciences Research Ethics Committee (JREC) and Medical Research Council of Zimbabwe were obtained. All participants gave written informed consent prior to recruitment. Confidentiality was maintained by the use of study numbers on the data collection sheet and also on the samples collected. All records were kept locked in a cupboard only accessible to the study team. All abnormal results and abnormal clinical assessments were communicated to the participants and referred to the usual attending physician.

8. RESULTS

8.1 Demographic data and baseline characteristics

124 study patients were enrolled in the study. Of the total study participants, two participants did not have serum creatinine results so they were excluded in the renal dysfunction analysis. A total 122 study participants were included in the final analysis. There were 86 (69.4%) female and 38 (30.6%) male participants. The mean age of the patients was 37.7 ±11.3 years. 51.7% of the patients were married. The mean weight (kg) and Body Mass Index (BMI) (Kg/m^2) for the group was 67.3 ±13.1 and 26.0 ±5.2 respectively. The mean systolic and diastolic blood pressures were 130.1 ±21.0 and 76.1±15.1 mmHg respectively. 17 of the participants had a high BP reading at the time of the clinical examination and most of these had a prior history of being on antihypertensive medication. The systolic blood pressure was greater than 160mmhg. Urine dipsticks were positive for protein in 11(8.9%) that is a 1+ or more on urinalysis. The median serum creatinine was 83.5µmol/l (IQR 69.6-99.2). The median CD4 count for the group was 447 cells/µmol (IQR 297-612) (TABLE2)

Table 2 Demographic and clinical features of study participants

Patient Characteristic	**N=124**
Age in years, mean ±sd	37.7±11.3
Females, n (%)	86(69.4)
Males, n (%)	38 (30.6)
Single	26 (21.7)
Married	62 (51.7)
Widowed	14 (11,7)
Divorced	18 (15.0)
Clinical measures	
SBP mmHg, mean ±sd	130.1±21.0
DBP mmHg, mean ±sd	76.1±15.1
High BP reading, n (%)	17 (13.9)
Weight in kgs, mean ±sd	67.3±13.1
BMI kg/m², mean ±sd	26.0±5.2
Clinical History	
History of O.I	38 (30)
Antihypertensive drugs	17 (13.7)
Family History of Renal failure n (%)	3 (2.4)
Laboratory measurements	
Urine dipstick protein positive +1, n (%)	11 (8.9)
Urine protein: creatinine median(IQR)	0.08 (0.04-0.23)
Serum creatinine (µmol/l), median (IQR)	83.5(69.6-99.2)
CD4 cell count, median (IQR)	447 (297-612)

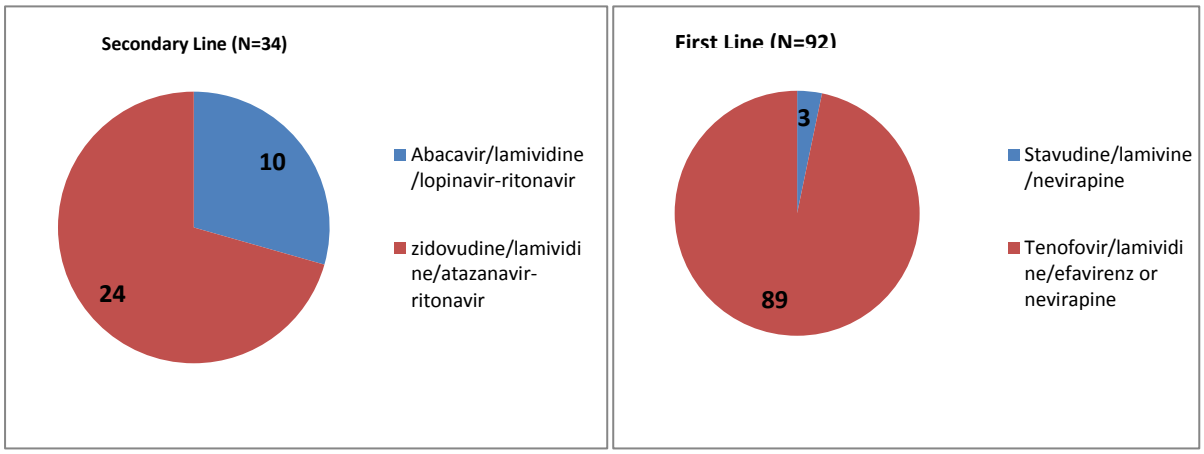
There were 35 (28.2%) with a previous history of tuberculosis, 2 (1.6%) with cryptococcal meningitis and 1 (0.8%) with Kaposi sarcoma. The history of hypertension was in 17 (13.9%) participants and 3 (2.4%) participants had diabetes mellitus. (TABLE 3)

Table 3 Clinical features

Clinical features	Frequency, n (%)
Tuberculosis	
Yes	35 *(28.2)*
No	89 *(71.8)*
Cryptococcal meningitis	
Yes	2 *(1.6)*
No	122 *(98.4)*
Pneumocystis jiroveci	
Yes	6 *(4.9)*
No	117 *(95.1)*
Kaposi sarcoma	
Yes	1 *(0.8)*
No	123 *(99.2)*
Diabetes mellitus	
Yes	3 *(2.4)*
No	121 *(97.6)*
Hypertension	
Yes	17 *(13.9)*
No	105 *(86.1)*

Most of the participants were on first line ART i.etenofovir, lamividine, nevirapine (NVP)/ efavirenz (EFV) 89 (96.7%) while 32 (25.8%) were on second line ART abacavir/zidovudine, lamividine, boosted lopinavir with ritonavir/ boosted atazanavir. (pie chart)

Pie chart Current Antiretroviral regimens



8.2 Renal Dysfunction

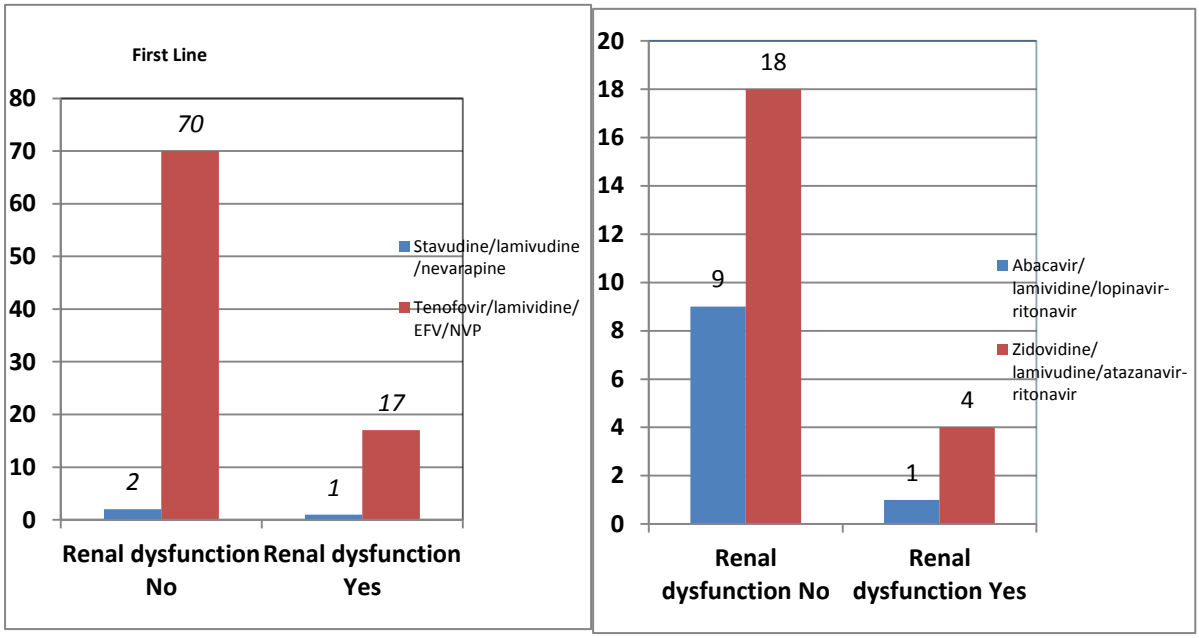
Renal dysfunction was defined as creatinine clearance less than 60ml/min. A total of 23/122(18.9%) had renal dysfunction. There was no significant difference in age distribution between patients with renal dysfunction (mean age 40.2±15.9 years) and those without renal dysfunction (mean age 37.2±10.1 years), p=0.268. Mild reductions, (CrCl 60-89) in creatinine clearance with proteinuria were found in 14 /121 (36%) participants; while16 (26%) had normal creatinine clearance (CrCl>90ml/min). Mild reduction in eGFR defined as creatinine clearance between 60-90mls/min were seen in 38 (31.2%) irrespective of proteinuria status (Table 5).

Table 4 Creatinine clearance and proteinuria

Creatinine clearance category	**Albumin category**			**Total**
	Normal	**Micro albuminuria**	**Macro albuminuria**	
Renal dysfunction, n (%)	10(43.5)	7(30.4)	6(26.9)	**23**
Mild to moderate, n (%)	24(63.2)	8(21.0)	6(15.8)	**38**
Normal, n (%)	45(73.8)	8(13.1)	8(13.1)	**61**
Total	79(64.8)	23(18.8)	20(16.4)	**122**

Seventeen participants on first line antiretroviral therapy which included tenofovir had renal dysfunction and four participants on second line which contained atazanavir as one of the combinations had renal dysfunction (graph)

Graph : Renal dysfunction and ART regimens



8.3 Factors associated with renal dysfunction

Univariate analysis of risk factors associated with renal dysfunction showed that male gender and presence of micro albuminuria were the only factors that were statistically significant (p value <0.05) (see table 6).Being married, previous history of an opportunistic infection, CD4 count and low BMI had p value>0.05.

Multivariate analysis showed that micro albuminuria continued to be statistically significant for the presence of renal dysfunction p value<0.049.

Table 6: Analysis of risk factors for renal dysfunction

Factor	Univariate analysis				Multivariate analysis	
	Renal dysfunction		OR(95% CI)	p-value	OR(95% CI)	p-value
	Yes	No				
Gender						
Female	11	73	1		1	
Male	12	26	3.06(1.21- 7.78)	0.019*	2.12(0.66-6.74)	0.205
Age group						
<40	9	59	1		1	
≥40	14	40	2.29(0.91-5.81)	0.080	3.79(0.99-14.50)	0.051
Marital status						
Married	11	49	1		1	
Single	6	20	1.34(0.43-4.11)	0.613	1.24(0.19-8.16)	0.822
Widowed	2	12	0.74(0.14-3.80)	0.721	3.24(0.41-25.66)	0.266
Divorced	2	16	0.56(0.11-2.78)	0.476	0.37(0.03-5.26)	0.460
TB						
No	18	69	1		1	
Yes	5	30	0.64(0.22-1.88)	0.416	0.76(0.18-3.22)	0.711
PCP						
No	21	94	1		1	
Yes	2	4	2.24(0.38-13.04)	0.370	6.49(0.46-91.22)	0.165
Hypertension						
No	19	84	1		1	
Yes	4	13	1.36(0.40-4.64)	0.623	0.61(0.13-2.92)	0.535
ART regimen						
First line	18	72	1		1	
Second line	5	27	0.74(0.25-2.19)	0.588	0.34(0.07-1.65)	0.181
CD4 category						
<200	3	9	1		1	
≥200	20	89	1.48(0.37-5.98)	0.579	3.86(0.57-26.12)	0.166
BMI category						
Normal	10	36	1		1	
Underweight	2	3	2.4(0.35-16.39)	0.372	5.03(0.42-59.81)	0.201
Overweight	5	46	0.39(0.12-1.25)	0.112	0.46(0.10-2.03)	0.305
Obese	6	14	1.54(0.47-5.05)	0.473	1.77(0.36-8.68)	0.481
Urine protein creatinine ratio						
normal	10	69	1		1	
micro albuminuria	7	16	3.02(1.00-9.15)	0.051	4.14(1.00-17.04)	0.049*
macroalbuminuria	6	14	2.96(0.92-9.47)	0.068	2.37(0.53-10.52)	0.256

*** Variables** statistically significant associated with renal dysfunction ($p < 0.05$)

9. Discussion

Renal dysfunction is a common sequel of HIV infection and it can be due to antiretroviral drugsor drugs used to treat certain opportunistic infections.[48] The prevalence of renal dysfunction in this study was 18.9% in HIV positive patients on HAART. The prevalence was higher compared to patients who were HAART naïve in the study done by Fana et al.[28] This could be explained by patients having been on ART for a longer time as cumulative exposure to ART has been shown to have an increased prevalence in renal dysfunction.[15] Given that this was a cross sectional study, patients with reversible causes of renal dysfunction may have been included. The prevalence is lower compared to a study done in Burundi which found renal dysfunction in 45.7%.[49] This could be explained by the differences in study populations, stage of HIV infection, definition of chronic kidney disease and the formula used to calculate creatinine clearance. A study done in Ethiopia[26] showed a prevalence of 12.9%, which is lower than the prevalence in this study. The demographic features of the Ethiopian study sample population were similar to this study. However, most participants in the Ethiopian study were receiving stavudine based regimens, whereas patients in this study received tenofovir based regime. The Ethiopian study only measured the urine dipstick protein compared to the present study which did a urine: protein creatinine ratio hence being able to identify early patients who do not have overt proteinuria. This could account for the higher prevalence shown in this study. In a study done in Uganda by Peters[25] et al, in which they followed up patients who had been started on ART and pre ART, prevalence of renal dysfunction was 20% as evidenced by a creatinine clearance between 25 and 59ml/min. After 24 months on ART, the proportion of participants with renal dysfunction decreased from 20% at baseline to 6%. Participants in this study did not receive tenofovir and the authors stated that the results from their study could not be extrapolated to

tenofovir based regimens without further evaluation. Another study done in Brazil[15] showing a prevalence of 8.4% was done on patients with undetectable viral loads and CD4 counts> 200cells/µml, that is patients who are quite stable. This could explain why the prevalence is lower than the current study. Current study participants had no viral load tests done, hence the possibility that some may not have been virologically suppressed and the HIV infection might have an effect on the high prevalence. The Brazil study showed that being on tenofovir and having been on antiretroviral therapy for a longer duration had a significant association with renal impairment. This is in accordance with other studies done in other settings that have shown tubular dysfunction developing in patients on tenofovir.

A study done by Reid and colleagues[27]was performed in Zimbabwe and Uganda. It showed a prevalence of 7% defined for patients with greater than stage 3 CKD. 30% of their participants were from Harare-Zimbabwe, and therefore the participants in their study had similar characteristics as those in the current study. The gender composition comprising of females was (69%) in this study and (65%) in Reid's study was almost similar. Age was also almost similar with an average age of 37.7 in this study and 36.2 in the study done by Reid et al. The number of participants on tenofovir in the current study was 89% while study by Reid had 74%, which was almost similar in both studies. The Cockcroft-Gault formula[46] was used in both studies to estimate the GFR. The participants in these two studies were almost similar however; the current study had other participants who had been on other ART regimens before being switched to a tenofovir based regimen and maybe this has a bearing on having a higher prevalence of renal dysfunction in the current study. Other studies have shown that time on HAART is significantly associated with CKD.[15] The study done by Reid did not test for tubular dysfunction as tenofovir is known to cause tubular dysfunction with

probably a normal GFR initially, which manifests as a Fanconi syndrome or nephrogenic diabetes insipidus.[52] One of the weaknesses of the current study was the lack of tests for tubular dysfunction, given that most of the participant were on tenofovir based regimen. The wide variation in prevalence of renal dysfunction in the different studies is partly due to use of different formulas to define renal dysfunction, number of study participants and variability in HIV virologic control.

In univariate analysis the factors associated with renal dysfunction in the current study were male gender and micro albuminuria. Micro albuminuria remained statistically significant in multivariate analysis (p= 0.049). Micro albuminuria has been shown to be closely related to developing renal impairment mainly in patients with hypertension and diabetes mellitus. Very few studies have been done to see if this happens to patients who are HIV positive. A study done by Mulomaet al[51] in Kenya recorded that proteinuria in HIV infected patients is associated with progressive renal impairment. A dipstick urinalysis maybe unreliable in tenofovir nephrotoxicity; this was shown in a retrospective chart review done by Sise and colleagues in which they were determining the pattern of proteinuria in patients with TDF nephrotoxicity.[52] In this retrospective chart review they confirmed that TDF nephrotoxicity is associated with a non-albumin proteinuria and a dipstick urinalysis might not be able to pick up TDF nephrotoxicity.

The current study did not show that being on tenofovir was statistically significant in causing renal dysfunction- p 0.492. This is similar to other studies that have been done to show that prevalence of renal dysfunction in patients on tenofovir is low.[27, 41] However, in all these studies tubular injury was not being tested hence the need specifically to do a study which looks at tubular injury. A study done by Labarga[53] et al showed that exposure to tenofovir is

associated with an increased risk over time of kidney tubular abnormalities in the absence of significant impaired glomerular function. Bone mineral loss can occur and there is a need to screen for tubular function parameters (glucosuria, hyperaminoaciduria, hyperphosphaturia, hyperuricosuria and β2 microglobubulinuria) in patients on tenofovir.

The current study had patients with a median CD4 count of 447 (IQR 297-612) and there was no association of renal dysfunction in those with a CD4 count <200 which is in contrast to other studies which have shown that low CD4 counts are associated with renal dysfunction.[26,50]The patients recruited in the study had been on ART for greater than 3 months hence a difference in other studies which were done in patients who were ART naïve. These patients' immune status might have improved somewhat due to the ART hence resulting in a low association of CD4 and renal dysfunction, as most patients in the study had been on ART for greater than 3 months. Three months is not sufficient time to have marked renal improvement in a patient unless the cause of the renal dysfunction was a reversible cause. Nadir CD4 counts where not documented in these patients hence there was no comparison to see how the immune status of the participants had changed over time.

10 STUDY LIMITATIONS

This cross sectional study had a few limitations. Creatinine and proteinuria was being measured at single point in time with no reference to any baseline renal status, so the study might have included patients with short term reversible causes of renal impairment.

The study did not also have information on baseline creatinine or eGFR as this information could have been used to compare renal function of the participant and the current values to

see if this was new onset renal dysfunction or the patient had already renal dysfunction from baseline.

Use of the Cockcroft-Gault formula is not properly validated in patients who are HIV positive and in black populations and might overestimate the degree of renal dysfunction.

The history of ART regimens as given by patientsmay not been accurately remembered and reports of any ART switches that may have been done may not be well documented, possibly leading to recall bias.

Tubular function was not tested in this study, to determine if patients on tenofovir had any tubular dysfunction as it has been shown that patients on tenofovir might have normal eGFR even with proven tubular dysfunction.

11. RECOMMENDATIONS

- Urine Protein: Creatinine ratio is recommended for patients on HAART as it picks up patients with early renal dysfunction.

- Those patients with micro albuminuria should be closely monitored as there is a risk of developing renal dysfunction.

- A longitudinal study is recommended to follow up patients who are on HAART and more comprehensive test including imaging, renal biopsy, hepatitis screens, viral load and tubular function be assessed on those patients who on screening have renal dysfunction and more so on patients on tenofovir.

12. CONCLUSION

Renal dysfunction was present in 18.9% of patients who are HIV positive andtaking HAART. The risk factor for renal dysfunction was micro albuminuria. Screening for micro albuminuria and estimation of creatinine clearance is recommended in patients on HAART. Regular screening for kidney disease using the urine protein creatinine ratio should be standard of care.

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12. APPENDICES

APPENDIX 1

Data collection sheet

1.	**Demographic features**				
1.1.	Study number				
1.2.	Date of Birth (DD/MM/YYYY)				
1.3.	Gender	Male		Female	
1.4.	Marital Status	Single	Married	Divorced	Widowed
2.	**Past Medical History (Tick V Where applicable)**				
2.1.	Tuberculosis	Yes		No	
2.2.	Cryptococcal Meningitis	Yes		No	
2.3.	PCP	Yes		No	
2.4.	Kaposi Sarcoma	Yes		No	
2.5.	Diabetes	Yes		No	
2.6.	Hypertension	Yes		No	
2.7.	Month and year of ART initiation				

	(MM/YYYY)			
3. Drug History				
3.1.	Anti-hypertensives			
3.2.	NSAID'S			
3.3.	Hypoglycaemic drugs			
3.4.	ART Regimen	First Line		
		Second line		
		Other		
4. Family history				
4.1.	Family History of kidney disease		Yes	No
5. Clinical Examination				
5.1.Blood pressure		Systolic mmHg		
		Diastolic mmHg		
5.2. Mass (kg)				
5.3. Height (m)				
5.3. Body Mass Index (BMI) (Kg/m2)				
6. Any other underlining conditions.				
6.1.				
6.2.				
6.3.				
6.4.				
6.5.				
7. Laboratory results				
7.1.	Urinary dipstick	Proteinuria	+ ☐	– ☐
		Haematuria	+ ☐	– ☐
		Leukocytes	+ ☐	– ☐
7.2.	Serum Creatinine (micromoles/l)			
7.3.	Calculated creatinine clearance (ml/min/1.73 m^2)			
7.4.	CD4 Count (Cells/mm^3)			
7.5.	Random blood glucose			

APPENDIX 2

ENROLMENT INFORMED CONSENT

PROTOCOL TITLE: Renal dysfunction in HIV positive patients on Highly Active Antiretroviral Therapy (HAART)

NAME OF RESEARCHER: Dr Patience Julia Maramba

PHONE: Mobile +263 773 655 776

INVITATION:

You are being invited to participate in this research study because you are infected with HIV (Human Immunodeficiency Virus)

The doctor- in-charge of this research study is Dr Patience J Maramba. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about the study. The doctor-in-charge will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study you will be asked to sign this consent form. You will get a copy to keep.

YOUR RIGHTS

Before you decide whether or not to volunteer for this study, you must understand its purpose, how it may help you, the risks to you, and what is expected of you. This process is called informed consent.

WHY IS THIS STUDY BEING DONE?

The kidneys are the organs in the human body that remove waste products. In patients who are HIV positive the kidneys function can be affected by different infections and also treatment given to patients. The purpose of this study is to determine the number of patients with HIV infection on antiretroviral therapy who also have evidence of kidneys not working well. Another purpose is to find factors associated with the presence of poor kidney function.

STUDY PROCEDURE

If you agree to participate the following information will be obtained from you:

Information about sex, age, marital status, when you started your antiretroviral therapy and all the different drugs you have taken, your medical and family history. You will have about 3 tablespoon of blood drawn to measure your CD4cell count (CD4 cells help your body to fight infection and are attacked by the HIV infection), urea and creatinine (substances normally excreted by the kidney but accumulate when kidneys are not working well).

About half a cup of urine will be collected and tested for protein by a test strip and some will be used to quantify the amount of protein in a laboratory.

DISCOMFORTS AND RISKS

There is minimal risk for being in the study. All the procedures that may be done on you are those that would be done routinely on anyone with the same condition as yours who is not in the study. You may need to spend a little bit of extra time for about 30 minutes at the clinic for the study staff to verify personal information about you and medical information from your hospital records.

Risks of drawing blood

Blood collection from a vein may cause pain at site of puncture. A bruise may form at the site. Infection and prolonged bleeding are very rare complications that can occur. Qualified personnel will collect the blood samples to prevent such complications.

Risks of collecting urine

You will pass urine in a secure private toilet facility. There is no risk expected to you in collecting urine.

POTENTIAL BENEFITS

There may not be immediate benefit to you now for participating in this study. This study will help researcher to learn more about function of the kidney on patients on antiretroviral therapy. If abnormalities are picked, your doctors will be informed and appropriate action will be taken. All information collected on other patients with a condition similar to yours will be combined and analysed.

STUDY WITHDRAWAL

You may choose not to enter the study or withdraw from the study at any time without loss of benefits entitled to you.

COSTS/ PAYMENT

There is no payment that is required from you if you take part in the study. The study will pay for study tests that will be done on you. You will not be paid for taking part in the study.

INJURY

It is not anticipated that you will be injured as a result of participating in this research as it requires collection of information only. Signing this consent form to participate in this research study does not take away any legal rights you may have in the case of negligence or legal fault of anyone who is involved with this study.

CONFIDENTIALITY OF RECORDS

We will make every effort to keep your research records confidential. Information about you obtained for this study will be kept confidential and will not be released without your written permission unless compelled by law.

Medical records that identify you and the consent form signed by you, may be reviewed by the following people:

- The Joint Parirenyatwa College of Health Sciences Research Ethics Committee
- The Medical Research Council of Zimbabwe (MRCZ).

  These are ethical bodies that ensure the safe conduct of research studies.
- Your records may also be reviewed by Study staff.
- The Department of Medicine of the University of Zimbabwe.

The results of this research study may be presented at meetings or in published articles. However, your name will not be used.

PROBLEMS/QUESTIONS

If you have questions about this study, you can ask now. If you have questions in future please contact:

Dr Patience J Maramba

Telephone number: +263 773655776

Physical Address: UZ Department of Medicine College of Health Sciences. Mazowe Road Harare.

If you have questions as a person who is taking part in a research study, you can call the secretary of the Joint Parirenyatwa College of Health Sciences Ethics Research Committee on 731000 ext. 2240 or the Secretary for Medical Research Council of Zimbabwe on 791792.

AUTHORIZATION

I have read this consent form or it was read and explained to me. I have been given the opportunity to ask questions. All the questions I asked have been answered to my satisfaction.

I understand the possible risks and benefits of this study. I know that being in this study is voluntary. I know I can stop being in the study at any time without it in any way affecting my further medical care.

I will get a copy of this consent form.

(Initial all the previous pages of the consent form)

_____

Participant's Name (Print)

_____ _____

Participant's Signature Date

_____

Participant's Thumb Print (If Unable to read)

_____

Witness's Name (Print)

(As appropriate)

_____ _____

Witness's Signature Date

_____ _____

Signature of Investigator Date

APPENDIX 3

ENROLMENT INFORMED CONSENT SHONA VERSION

GWARO RETENDERANO

PROTOCOL TITLE: Renal dysfunction in HIV positive patients on Highly Active Antiretroviral Therapy (HAART)

ZITA REMUTSVAKIRIDZI|: Dr Patience Julia Maramba

NHAMBA DZANHARE: +263 773 655 776

KOKORODZO

Murikukokwa kupinda mutsvakiridzo ino nekuti mune utachiona hwe HIV hunokonzera chirwere chemukondombera.

Chiremba arikuita tsvakiridzo iyi anonzi Patience Julia Maramba. Musatimafunga kupinda mutsvakiridzo ino, munofanira kuziva donzvo retsvakiridzo iyi, kuti zvinokubatsirai chii, njodzi dzingangoitika uye zvinotarisirwa kubva kwamuri.

Gwaro rino rinoratidza kuti matipa mvumo yekuti tikupinzei mutsakiridzo iyi. Rinokupai ruzivo nezvetsvakiridzo iyi. Chiremba mukuru mutsvakiridzo iyi achataura nemi pamusoro petsvakiridzo iyi. Makasununguka kumubvunza chero nguva yamungaite mibvunzo paongororoiyi. Kana mukabvuma kupinda mutsvakiridzo iyi muchakumbirwa kuti muise runyoro rwenyu rwetendero pafomu rino. Mukadaro muchapihwa rimwe fomu rakafanana nerino kutimurichengete.

KODZERO DZENYU

Musatimafunga kupinda mutsvakiridzo ino, munofanira kuziva donzvo racho, kuti zvinokubatsirai chii, njodzi dzingangoitika uye zvinotarisirwa kubva kwamuri.

DONZVO RETSVAKIRIDZO

Itsvo dzinoshanda kubvisa tsvina mumuviri memunhu . Muvarwere vane utachiona hwe HIV itsvo dzinogona kukanganisika nezvinhu zvakasiyana siyana uye mishonga yavangamwe. Donzvo rechidzidzo chino kuera uwandu hwevanhu vane hutachiwona hweHIV varipachirongwa vane zviratidzo zvekuti itsvo dzavo hadzizikushanda zvakanaka. Rimwe donzvo nderekudakudzidza ukama hungavepo pakati pezvinhu zvakasiyana siyana nekusashanda zvakanaka kweitsvo

ZVICHAITWA MUTSVAKIRIDZO

Kana mukabvuma kupinda mutsvakiridzo iyi muchakumbirwa kuita zvinotevera:

Muchavhunzwa makore ekuberekwa, kutimakaroora kana kuroorwa, gore ramakakatanga kupinda muchirongwa uye mishonga yese yamakapihwa, nhoroondo yeutano hwenyu uye yekumhuri kwamakaberekwa. Muchatorwa zvipunu zvitatu zveropa. Ropa iri richashandiswa kuera huwadu hwemasoja emumuviri anodzivirira zvirwere (CD4cell count), uye urea necreatinine (izvi zvinhu zvinogadzirwa mumuviri yenyu zvinoraswa mazuva ose neitsvo dzenyu ,zvinoungana mumuviri kana itsvo dzisingashandi zvakanaka). Tichatora weti yenyu ingawanda kusvika pakati nepakati pekomichi. Weti iyi ichaoongororwa nekapepa kanonyikwa mairi kanoratidza kuwanda kweprotein.

KUSAGADZIKANA NENJODZI (*DISCOMFORT AND RISKS*)

Zvine njodzi shomanana chaizvo kuve mutsvakiridzo ino. Zvose zvichaitwa pamuri zvinoitwa nguva dzose pavanhu vanechirwere chinenge chenyu vasiri mutsvakiridzo. Tsvakiridzo iyi ingangotora zvikamu zvitatu zvemaminitsi mukiriniki kana vana chiremba vachiongorora nekubvunza mubvunzo.

Njodzi mukutorwa ropa

Pamunotorwa ropa zvinogona kurwadza kana kuita kachironda kadiki pamunenge mabaiwa. Pane kamukana kadokwane kekuti mungango ramba muchibuda ropa kana kutapura hutachiwona. Vanhu vakadzidzira basa iro ndivo vachatora ropa kuti izvi zvidzivirirwe

Njodzi mukuto rwaweti

Muchakumbirwa kuti murase mvura muchichengetedza muchigaba chamuchapiwa. Izvi muchaita muri muchimbuzi chakachengetedzwa uye muri pachezvenyu. Hapana njodzi inotarisirwa kuti ingakuwirai mukuita izvi.

ZVAMUNGAWANA *(BENEFITS)*

Hapana zvamungawa nane kupinda mutsvakiridzo pari zvino, asi ruzivo ruchawanikwa kubva mutsvakiridzo runogona kubatsira vamwe vane chirwere chinenge chenyu munguva dzinotevera. Kana paine zvaonekwa zvingada kurapwa, machiremba enyu achaziviswa matanho akakodzera agotorwa. Ruzivo ruchawanikwa kubva kune umwe neumwe ane utachiona hwe HIV achapinda mutsvakiridzo iyi ruchasanganiswa roongororwa.

ZVAMUNGAITA KUNZE KWEKUVE MUTSVAKIRIDZO

Munogona kusarudza kusapinda mutsvakiridzoino. Kana mukasapinda mutsvakiridzo muchangoramba muchirapwa kukiriniki ino.

KUBUDA MUTSVAKIRIDZO

Munogona kusarudza kusapinda mutsvakiridzo kana kubuda panguva ipi neipi zvayo. Izvi hazvikanganise kurapwa kwenyu kana zvimwe zvamunekodzero yekuitirwa kana kuwana.

MURIPO KANA KURIPWA

Hapana zvinotarisirwa kuripwa kana mukapinda mutsvakiridzo. Hamuripire zvamuchaitwa zvinoenderana nechidzidzo ichi. Hapana mari yamuchapiwa mukapinda mutsvakiridzo.

KUKUVARA

Hatitarisire kuti pane kukuvara kungaitika nekuve mutsvakiridzo ino, nekuti tinongoda kutora ruzivo chete. Kusaina gwaro rino hakubvise kodzero dzamungavenadzo pamutemo kana musina kubatwa zvakanaka nevarikuita tsvakiridzo.

KUCHENGETEDZWA KWEZVINYORWA

Tichaedza nepatinogona kuchengetedza zvinyorwa zvetsvakiridzo zvinechekuita nemi. Hapana zvinechekuita nemi zvichashambadzirwa musina kutendera kunze kwekunge zvichidiwa nemutemo. Zvinyorwa zvine zita renyu zvinogona kutariswa nevanhu ava:

- VeJoint Parirenyatwa College of Health Sciences Research Ethics Committee (JREC)
- VeMedical Research Council of Zimbabwe (MRCZ). Aya mapazi anoona nezvekufambiswa kwetsvakiridzo.
- Vashandi vetsvakiridzo
- Bazire Dapartment of Medicine reUniversity yeZimbabwe

Ruzivo ruchawanikwa mutsvakiridzo runogona kushambadzwa mumisangano kana mumagwaro nhawu. Asi zita renyu harizoshambadzirwi.

DAMBUDZIKO KANA MIBVUNZO

Kana mune mibvunzo bvunzai iye zvino. Kana mukazoita mibvunzo munguva inotevera munogona kubvunza: Dr Patience Julia Maramba

Nhamba dzenhare:+ 263 773 655 776

Pavanowanikwa: University of Zimbabwe Department of Medicine, College of Health Sciences. Mazowe Road Harare.

Kana mune mibvunzo nezvekodzero dzenyu semunhu ari muchidzidzo ridzai nhare

- Munyoriwe Joint Parirenyatwa College of Health Sciences Ethics Research Committee pa +263 4 731000 ext. 2240 kana
- Munyori weMedical Research Council of Zimbabwe pa +263 4 791792.

MVUMO

Ndaverenga kana kuti ndaverengerwa nekutsanangurirwa zviri mugwaro rino. Ndapiwa mukana wekubvunza. Mibvunzo yese yapindurwa zvandigutsa. Ndinonzwisisa zvakaipa zvingangoitika nezvakanaka zvandingawana mutsvakiridzo ino. Ndinoziva kuti kupinda mutsvakiridzo kuda kwangu. Ndinoziva kuti ndinogona kubuda mutsvakiridzo zvisingakanganise kurapwa kwangu munguva inotevera.

Ndichapiwa rangu gwaro rakafanana nerino.

(Sainai ose mapepa egwaro rino).

_____

Zita remurwere

_____ _____

Saini yomurwere Zuva ranhasi

_____

Mucherechedzo wemunwe wenyu mukuru

(Kana musingagone kunyora)

_____

Zita remupupuri

_____ _____

Saini yemupupuri Zuvaranhasi

_____ _____

Saini yachiremba vetsvakiridzo Zuvaranhasi

APPENDIX 4

The Modified Jaffe Method: measurement of serum and urine creatinine concentration. A precise volume of sample, 30µl of serum or 10 µl of urine is injected in a reaction cup containing an alkaline picrate solution. At an alkaline solution, creatinine combines with picric acid to form an orange red coloured complex. The absorbency increase is directly proportional to the concentration of creatinine.

APPENDIX 5

Microprotein: measurement of urine protein

Microprotein reagent is used to measure protein concentration by a timed endpoint. Protein in the sample reacts with pyrogallol red (PR) mobylate (Mo) to form a purple colour complex. The SyndronCx System automatically proportions the appropriate sample and reagent volumes in a curette. The system monitors the change in absorbance at 600 nanometres. This change in absorbance is directly proportional to the concentration of protein in the sample and is used to calculate and express the protein concentration.

APPENDIX 6

CD4 T cell counting with Partec CD4 easy count kit

Add 20µl whole blood to a test tube then add 20µl of CD4 mAb PE (Partec CD4 easy count kit). Mix gently and incubate 15 minutes at room temperature in the dark. Add 800µl of no lyse buffer (Partec CD easy kit) and shake gently. Run prepared blood sample on a Partec flow cytometer.

Method

- Display 1 parameter histogram and “select log 3” for fluorescence

- Select TRIGGER= fluorescence parameter
- Set dilution factor 1 (for Cyflow Counter)
- Shake the bottle thoroughly before using it
- Take a sample of 850µl of the Count Check Beads green into a sample tube.
- Let the system run in Count mode until it stops

Results

- Select VIEW, REGION STATISTICS in order to display the beads concentration per ml below the plots