

Incidence of Nephropathy in HIV Infected Patients Receiving Highly Active Antiretroviral Therapy at Newlands Clinic: A Retrospective Study

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Abstract

Introduction: HIV infected patients on antiretroviral therapy (ART) are at risk of developing nephropathy and therefore require monitoring of renal function. Some medications used in the management of HIV, opportunistic infections (OIs) and other co-morbidities are nephrotoxic and may further compromise renal function, underlining the importance of regular monitoring of renal function. This study was designed to determine the incidence of nephropathy in HIV infected patients on antiretroviral therapy (ART) at Newlands Clinic and to determine the associated risk factors. **Methodology:** A retrospective cohort study was conducted involving 1986 HIV-1 infected participants who were commenced on ART between January 2007 and December 2013 at Newlands Clinic. The majority of participants were female (1340 (67.5%)). All participants were aged 18 or older at ART commencement. Participants with pre-existing nephropathy at baseline were excluded. Nephropathy was defined as two consecutive calculated creatinine clearances (CrCl) less than 60 ml/min by the Cockcroft-Gault equation, or two consecutive urine dipsticks positive for protein (≥ 30 g/L albumin). Data collected during routine patient visits were exported from the clinic's database and analysed for incidence of nephropathy and risk factors. **Results:** During the follow-up period, 93 of the 1986 participants (4.7%) developed nephropathy. The estimated incidence rate (IR) of nephropathy was 1.45/100 person years (CI: 1.17 - 1.78). In the multivariate analysis, statistically significant risk factors were baseline age > 45 (HR 2.30, CI: 1.50 - 3.55), diabetes mellitus (HR 4.12, CI: 1.75 - 9.69), pulmonary tuberculosis (HR 2.00, CI: 1.28 - 3.12), and HIV wasting syndrome (HR 2.72, CI: 1.30 - 5.68). **Conclusion:** The incidence of nephropathy was low in this cohort. The traditional risk factors for renal disease; older age and diabetes mellitus were significant, as well as HIV wasting syndrome and pulmonary tuberculosis. HIV care should be complimented with proper diabetic care and patients that develop pulmonary tuberculosis, HIV

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wasting syndrome or are initiated on ART above 45 years require regular monitoring for early detection of nephropathy.

Keywords

Zimbabwe, Nephropathy, ART Management, HIV, Creatinine Clearance

1. Introduction

Among HIV infected patients, nephropathy can be caused by HIV related and non-HIV related pathologies. Non-HIV related pathologies include hypertension, diabetes mellitus, atherosclerosis, toxicities of medicines, as well as other infections [1]. HIV-associated nephropathy (HIVAN) is the most common form of kidney disease found in the HIV-infected population [2]. It is a unique clinical and pathological entity thought to be secondary to direct HIV infection of renal cells [3]-[5].

HIVAN is more common in patients with African ancestry due to a genetic variation in the APOL1 gene on Chromosome 22 and is common in African chromosomes but absent from European chromosomes [6]-[8]. Glomerular and renal epithelial cells are the primary targets of HIV pathogenesis in the kidney. The essential pathologic process is dysregulation of the epithelial cell cycle with increased proliferation, apoptosis, cellular dedifferentiation, and altered cellular polarity [5] [9]. Gerntholtz *et al.* found HIVAN in 27% of patients who had kidney biopsies done, and HIV immune complex kidney disease (HIVICK) in 21% in a South African study [6].

In the United States of America, progression to End Stage Renal Disease (ESRD) was found to be six-fold higher in HIV infected veterans of African descent compared to other races [10]. In a cohort study performed in Baltimore, Maryland assessing incidence of CKD, glomerular filtration rate slope and progression to ESRD in 4259 participants (78.2% African American), Lucas *et al.* found a CKD incidence of 11.2 per 1000 person-years. African American participants developed ESRD markedly faster than did white participants (HR, 17.7 [95% CI, 2.5 - 127.0]) [11].

The widespread use of antiretroviral therapy (ART) has influenced the epidemiology of HIV related kidney disease (HIVAN) by reducing mortality rates of ESRD among HIV infected individuals as well as incidence of HIVAN even though the protective effect of ART was only partial [6] [12]-[14]. Late initiation of ART has been suggested as a possible cause of poor renal outcomes [7] [14]. Antiretroviral drugs such as tenofovir (TDF), which is part of the preferred first line regimen in Zimbabwe, have been shown to cause renal toxicity, particularly proximal renal tubular dysfunction (PRTD) [15]-[18]. TDF together with indinavir (IDV), are the antiretroviral agents mostly associated with kidney toxicity since both are excreted via the kidney [19]-[26].

Cumulative exposure to antiretroviral medications TDF, IDV, Atazanavir (ATV) and Lopinavir/r (LPV/r) has been shown to increase risk of CKD in a cohort study by Mocroft *et al.* which included 6843 HIV infected individuals [22]. Participants in this study were from 103 centres in Europe, Israel and Argentina. The majority of them were male (75.1%) and Caucasian (85.5%). Incidence of CKD in this study was 1.05 per 100 person-years follow-up.

Other comorbidities such as cardiovascular disease, hypertension and diabetes mellitus have been known to be associated with chronic kidney disease (CKD) and ESRD among HIV negative individuals, and this association is also true among HIV infected individuals [27]-[30]. A combined cross sectional and one year follow up study where HIV infected participants were screened for proteinuria or significant impairment of glomerular function and then 424 of those that were negative in the screening were followed up for one year was performed in Tokyo, Japan. In this study Ando *et al.* found that HIV infected diabetic patients were four times likely to have tubular damage than HIV infected non-diabetics. They underscored the importance of urine protein screening for early detection of renal tubular damage [31].

Aging has been identified as one of the risk factors for CKD among HIV infected patients with increases in prevalence being more pronounced among HIV infected veterans than non-infected [32] [33].

Medications implicated in eliciting kidney injury include prophylactic cotrimoxazole when administered concomitantly with TDF in patients with low CD4+ cell counts [34]. Nonsteroidal anti-inflammatory drugs

(NSAIDs) and rifampicin may cause acute interstitial nephritis in patients. NSAIDs may also promote prerenalazotaemia in patients with true or effective intravascular volume depletion [21]. Antimicrobials used to treat opportunistic infections such as amphotericin B, acyclovir, foscarnet and pentamidine may also be nephrotoxic. Early detection and discontinuation of these antimicrobials can help avert kidney failure [23].

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), two groups of anti-hypertensive drugs, have been shown to have a protective effect on the kidney [35]. Use of these nephroprotective drugs as the preferred first line treatment for hypertension has been advocated for in the Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America [36]. There has been overwhelming evidence demonstrating better renal outcomes in patients treated with ACEIs and ARBs compared to the other classes of antihypertensive drugs, and the protective effect has also been shown in HIV infected individuals [35] [37]. It should be noted though that ACEIs are contraindicated in patients with known or suspected renovascular disease unless blood pressure control cannot be attained by other classes of antihypertensive medication. They should also be used with caution in patients with peripheral vascular disease and severe generalised atherosclerosis [38].

The American Primary Care Guidelines for the Management of Persons Infected with HIV note that kidney function may be abnormal in up to 30% of HIV infected patients. In that respect, they recommend that a baseline urinalysis and calculated creatinine clearance (CrCl), especially in black HIV-infected patients and those with advanced disease or comorbid conditions. They also recommend that urinalysis and CrCl should be performed prior to initiating drugs such as TDF or IDV that have the potential for nephrotoxicity [39]. Furthermore, Gupta *et al.* recommend biannual monitoring of renal function in patients receiving IDV or TDF [36].

There is currently no information on the incidence of nephropathy in patients receiving ART in Zimbabwe. The current Zimbabwean National ART Guidelines do not give concise instructions on the recommended frequency of laboratory monitoring of renal function in patients receiving ART or in those awaiting ART initiation.

The majority of published studies related to kidney disease have focused mainly on prevalence and not incidence probably because data on ART experiences in resource limited settings where HIV is more prevalent is only becoming available now as the scale up of ART continues to improve ART coverage. There is, therefore an unknown proportion of HIV infected patients receiving ART in Zimbabwe who are at risk of developing nephropathy due to the various etiologies of nephropathy among HIV infected individuals. These patients are also at risk of drug toxicities secondary to impaired renal function and may progress to end-stage renal failure. The inability to detect nephropathy in the early stages results in prolonged exposure to the offending medication and lack of appropriate dose adjustment. ART in resource limited settings is often given in fixed drug formulations, making dose adjustment in patients with nephropathy extremely difficult if not impossible.

2. Methods

An observational retrospective cohort study to determine the incidence of, and factors associated with nephropathy in HIV infected patients on ART at Newlands Clinic.

Data for 1986 participants who were HIV infected, aged above 18 years and commenced ART between 1 January 2007 and 31 December 2013 were analysed. Participants with pre-existing nephropathy at baseline were excluded. Nephropathy was defined as two consecutive CrCl measurements less than 60ml/min or two consecutive urine dipsticks that were positive for protein.

Secondary data were extracted using SQL Server 2012 from the clinic's electronic medical record, ePOC[®]. The database is used by the clinic staff as a point of care electronic medical record in the clinical care of patients, it is password protected and patient confidentiality for the study was ensured by the use of anonymised codes. The following data were extracted from the database: CrCl determined by the Cockcroft-Gault equation, urine protein measured with Roche Combur⁹ and Combur¹⁰ urine dipsticks, demographic data, diagnoses and medications. The SQL output was exported to Microsoft Excel, and then imported into STATA 12.0 where cleaning and analysis was done.

Participants who developed nephropathy were followed up from the date of the first CrCl measurement or urine dipstick until the date with the first of two consecutive abnormal measurements. Follow up of participants who did not develop nephropathy was censored at the date of the last laboratory measurement. The criterion defining a nephropathy with the earliest date was used *i.e.* either CrCl or proteinuria.

The statistical analyses used were the two sample test of proportions, Wilcoxon Rank Sum test to compare the medians of continuous variables and the Cox regression model for multivariate analysis. Data were regarded as

statistically significant when the P -value was <0.05 (two-tailed test).

As secondary data was used in this study, no major risks were posed to the participants. There were also no direct benefits to the participants but the results will lead to improved care of HIV infected individuals.

The study was approved by the Newlands Clinic Research team, the Joint Parirenyatwa Hospital and College of Health Sciences Research Ethics Committee (JREC Ref:230/13), the Biomedical Research and Training Institute (BRTI) Institutional Review Board (IRB) and the Medical Research Council of Zimbabwe (MRCZ/B/589).

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3. Results

A total of 1986 participants were included in the study whose total follow up time was 6411 person years. Out of the 1986 participants, ninety three (4.7%, $n = 93/1986$) participants developed nephropathy. Of these ninety three, sixty one (65.6%, $n = 61/93$) were classified as defined by two consecutive urine screen tests positive for proteinuria, while 32 (34.4%) were classified as defined by two consecutive CrCl results <60 ml/min calculated using the Cockcroft-Gault equation. The classification was mutually exclusive.

The estimated incidence rate of nephropathy in the study population was 1.45/100 person years (CI: 1.17 - 1.78). The Kaplan-Meier survival estimate for development of nephropathy over time in this cohort is shown in **Figure 1**. When disaggregated by sex, the incidence was higher among males (2.06/100 person years (CI: 1.47 - 2.80)) than females (1.19/100 person years (CI: 0.89 - 1.55)), but male sex was not a statistically significant independent risk factor.

Figure 2 illustrates the baseline demographic characteristics of the participants included in the study. Two thirds of the study population were female. There was a statistically significant difference between baseline ages of male participants (Median: 39; IQR: 34 - 45) and female participants (Median: 35; IQR: 30 - 41) baseline age with males being older ($p < 0.01$).

In the univariate analysis of sex as a risk factor, being male was a statistically significant risk factor (RR: 1.57; CI: 1.05 - 2.33; $p: 0.03$). Among the age groups, significant risk groups were participants aged 46 - 55 years (RR: 1.63; CI: 1.01 - 2.63; $p: 0.045$) and those above age 55 years (RR: 4.39; CI: 2.61 - 7.40; $p: < 0.01$). Participants

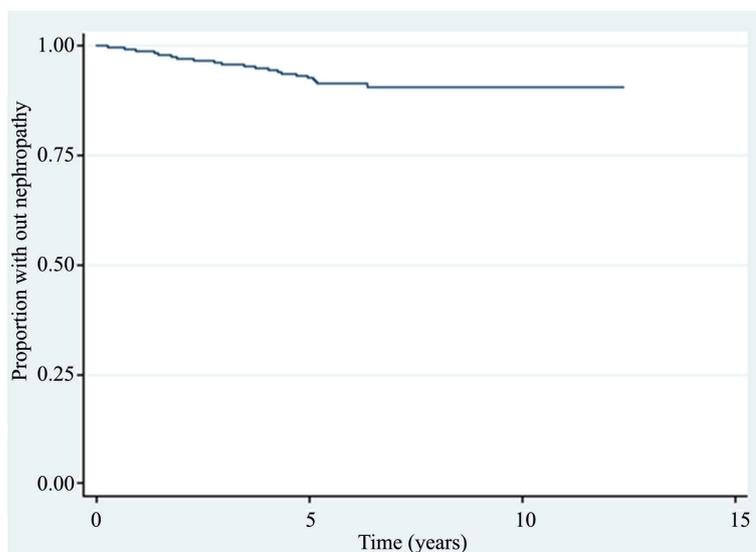


Figure 1. Kaplan-Meier survival estimate showing the development of nephropathy over time beginning at ART commencement.

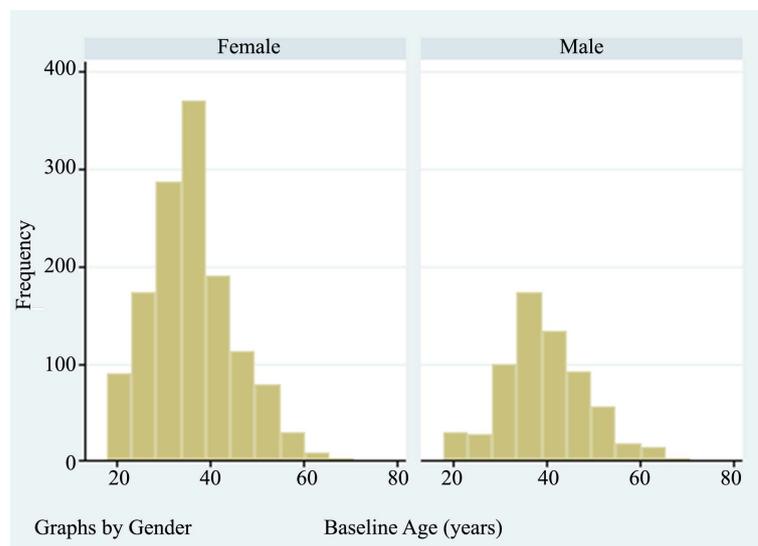


Figure 2. Baseline age distribution of female and male participants.

that developed nephropathy had a higher median baseline age (Median: 44; IQR: 37 - 56) than those that did not (Median: 40; IQR: 35 - 47) and this difference was statistically significant ($p = 0.01$).

Baseline clinical characteristics and results of their univariate analysis summarised in **Table 1**. The majority of participants (58.1%) presented to the clinic in early stages of disease *i.e.* WHO stage 1 and 2. Male patients presented later with more severe immunosuppression compared to female patients. A higher proportion of males (48.2%) presented with WHO stage 3 or 4 defining conditions, compared to 38.9% females. Baseline CD4+ cell counts were significantly lower for males than females ($p < 0.01$), with 57.6% having a baseline CD4 count ≤ 200 compared to 42.2% of females.

Tuberculosis was the most common opportunistic infection with 332 (16.7%) participants having been diagnosed with pulmonary tuberculosis and 110 (5.5%) extrapulmonary tuberculosis. Hypertensive patients constituted 11.6% ($n = 231/1986$) of the cohort.

Baseline WHO stage 3, pulmonary tuberculosis, extrapulmonary tuberculosis, oesophageal candidiasis, HIV wasting syndrome, diabetes mellitus and hypertension were statistically significant risk factors. The median baseline CD4+ cell count was higher among patients without nephropathy (Median: 214; IQR: 113 - 334) than those with nephropathy (Median: 156; IQR: 83 - 322) but this difference was not statistically significant.

None of the participants who developed nephropathy had a history of pneumocystis jiroveci pneumonia (PCP).

The most commonly prescribed NSAIDs were Diclofenac and Ibuprofen. Ciprofloxacin was the most commonly prescribed fluoroquinolone with almost half the patients having received a prescription, and none of the participants that developed nephropathy having received norfloxacin or ofloxacin. The commonly prescribed ACEI was captopril. One participant received enalapril while none received losartan. The majority of participants (96.5%) received TDF containing ART regimens, while none received IDV. Treatment characteristics are summarised in **Table 2**.

In the univariate analysis of treatment risk factors summarised in **Table 2**, only exposure to indomethacin among the NSAIDs was a statistically significant risk factor. Exposure to any of the antibiotics or the antiviral acyclovir was not a statistically significant risk factor. Exposure to ACEI captopril was also a significant risk factor (RR: 4.35; CI: 2.06 - 9.18; $p < 0.01$). Exposure to any of the antiretrovirals was not a statistically significant risk factor.

Diabetes mellitus, pulmonary tuberculosis, HIV wasting syndrome and age greater than 46 years were the statistically significant risk factors in the Cox regression model (Breslow method for ties) for multivariate analysis shown in **Table 3**. When the age groups above 45 years were disaggregated, the age group above 55 years had a higher hazard ratio (HR: 3.55, CI: 1.92 - 6.53, $p < 0.01$).

1784 (90.0%) participants were retained in the care at the end of the study. Participant outcomes are summarised in **Table 4**.

Table 1. Clinical characteristics of HIV infected participants enrolled at Newlands Clinic between January 2007 and December 2013; and univariate analysis results. N = 1986.

Characteristic	Total n (%)	Nephropathy n (%)	No Nephropathy n (%)	RR	CI	p-Value
Severity of Immunosuppression						
Baseline WHO Stage						
1	633 (32.3)	18 (19.6)	615 (33.0)	0.51	0.31 - 0.84	0.01
2	505 (25.8)	20 (21.7)	485 (26.0)	0.8	0.49 - 1.29	0.36
3	638 (32.6)	42 (45.7)	596 (31.9)	1.74	1.17 - 2.59	0.01
4	182 (9.3)	12 (13.0)	170 (9.1)	1.46	0.81 - 2.63	0.2
Baseline CD4 Count (cells/ μ L)-Median (IQR)	212 (112 - 333)	210 (162)	243 (174)			0.04
Opportunistic Infections						
Cryptococcal Meningitis	34 (1.7)	3 (3.2)	31 (1.6)	1.91	0.64 - 5.74	0.25
Pulmonary Tuberculosis	332 (16.7)	34 (36.6)	298 (15.7)	2.87	1.91 - 4.30	<0.01
Extrapulmonary Tuberculosis	110 (5.5)	10 (10.8)	100 (5.3)	2.05	1.10 - 3.85	0.02
Oesophageal Candidiasis	81 (4.1)	9 (9.7)	72 (3.8)	2.53	1.31 - 4.83	<0.01
Other AIDS Defining Conditions						
Severe Weight Loss	33 (1.7)	1 (1.1)	32 (1.7)	0.64	0.09 - 4.48	0.65
HIV Wasting Syndrome	58 (2.9)	9 (9.7)	49 (2.6)	3.56	1.89 - 6.73	<0.01
Kaposi Sarcoma	15 (0.8)	1 (1.1)	14 (0.7)	1.43	0.21 - 9.59	0.72
Comorbidities						
Diabetes mellitus	28 (1.4)	6 (6.5)	22 (1.2)	4.82	2.3 - 10.1	<0.01
Hypertension	231 (11.6)	20 (21.5)	211 (11.2)	2.08	1.29 - 3.34	<0.01

rised in **Table 4**. The proportion of participants deceased was higher among those that developed nephropathy (17/93) than in those that did not (60/1890) ($p < 0.001$).

4. Discussion

Our study demonstrated a low incidence rate of nephropathy (1.45/100 person-years) which was consistent with that found in other studies by Lucas *et al.* (CKD 12.5/1000 person-years among African American participants) and Mocroft *et al.* (1.05/100 person-years) [11] [22].

We identified diabetes mellitus, older age, a diagnosis history of tuberculosis and HIV wasting syndrome as significant independent risk factors for nephropathy. This is a confirmation of what has been shown previously in different populations. A diagnosis of pulmonary tuberculosis is a WHO stage 3 conditions, and that of HIV wasting syndrome is a WHO stage 4 condition. This suggests that the underlying cause is a longer interval of untreated HIV infection although the use of rifampicin in patients with tuberculosis is also a documented risk factor for nephropathy [40] [41].

The younger age of female participants compared to males might in part be explained by the national Prevention of Mother to Child Transmission (PMTCT) program which provides routine Provider Initiated HIV Testing and Counselling (PITC) to all pregnant women in Zimbabwe [18] [42]. Since the majority of pregnant women are in the 20 - 24 age group, this programme facilitates the enrolment of women into ART clinics at a younger age, and young mothers become beneficiaries of this facility [43]. As a result, male patients were not only older but also had lower CD4+ cell counts and a greater proportion of them had WHO stage 3 and 4 conditions than their female counterparts.

Table 2. Medications characteristics of HIV infected participants enrolled at Newlands Clinic between January 2007 and December 2013; and univariate analysis results. N = 1986.

Medications ^a	Total n (%)	Nephropathy n (%)	No Nephropathy n (%)	RR	CI	p-Value
Any NSAIDs	1406 (70.8)	63 (67.7)	1343 (70.9)	0.87	0.57 - 1.32	0.51
Aspirin	20 (1.0)	2 (2.2)	18 (1.0)	2.16	0.57 - 8.17	0.23
Diclofenac	1294 (65.2)	58 (62.4)	1236 (65.3)	0.89	0.59 - 1.33	0.56
Ibuprofen	701 (35.3)	28 (30.1)	673 (35.6)	0.79	0.51 - 1.21	0.28
Indomethacin	244 (12.3)	16 (17.2)	228 (12.0)	1.48	0.88 - 2.50	0.14
Antibiotics						
Rifampicin	183 (10.2)	11 (11.8)	172 (9.1)	1.32	0.72 - 2.43	0.37
Isoniazide	184 (9.2)	11 (11.8)	173 (9.1)	1.31	0.71 - 2.41	0.38
Any Fluoroquinolones	814 (41.0)	45 (48.4)	769 (40.6)	1.35	0.91 - 2.01	0.14
Ciprofloxacin	813 (40.9)	45 (48.4)	768 (40.6)	1.35	0.91 - 2.01	0.13
Antivirals						
Acyclovir	561 (28.2)	32 (34.4)	529 (28.0)	1.33	0.88 - 2.02	0.17
Anti-hypertensives						
ACEI	49 (2.5)	7 (7.5)	42 (2.2)	3.22	1.57 - 6.59	<0.01
Captopril	31 (1.6)	6 (6.5)	25 (1.3)	4.35	2.06 - 9.18	<0.01
Antiretrovirals						
Tenofovir	1862 (93.8)	56 (60.2)	1806 (95.4)	0.1	0.07 - 0.15	<0.01
Abacavir	116 (5.8)	6 (6.5)	110 (5.8)	1.11	0.50 - 2.50	0.8
Atazanavir	104 (5.2)	1 (1.1)	103 (5.4)	0.2	0.03 - 1.40	0.07
Lopinavir/r	196 (9.9)	7 (7.5)	189 (10.0)	0.74	0.35 - 1.58	0.44

^aSome patients received more than one medication in each of the classes at different times. Records represent patients that received at least one prescription of each medication.

Table 3. Multivariate analysis for independent risk factors.

Risk Factor	HR	CI	p-Value
Male	1.42	0.93 - 2.17	0.107
Diabetes mellitus	3.17	1.28 - 7.87	0.013
Hypertension	1.32	0.75 - 2.34	0.338
Pulmonary Tuberculosis	1.84	1.14 - 2.99	0.013
Extrapulmonary Tuberculosis	1.35	0.61 - 2.98	0.461
HIV Wasting Syndrome	2.55	1.19 - 5.42	0.015
Captopril Prescription	1.58	0.63 - 3.96	0.33
Age > 46 (years)	2.00	1.26 - 3.18	0.003
WHO stage 3 or 4	1.16	0.73 - 1.85	0.525

Table 4. Participant outcomes.

Patient Outcome	Nephropathy n (%)	No Nephropathy n (%)	Total n (%)
Active	72 (77.4)	1712 (90.6)	1784 (90.0)
Deceased	17 (18.3)	60 (3.2)	77 (3.9)
Lost to Follow Up	1 (1.1)	41 (2.2)	42 (2.1)
Stopped ART	0 (0.0)	3 (0.2)	3 (0.2)
Transferred Out	3 (3.2)	74 (3.9)	77 (3.9)
Total	93 (100)	1890 (100)	1983 (100) ^b

^bThree patients did not have a patient state assigned.

The limitations of this study primarily arise from the retrospective design. More precise measurements like urine and plasma phosphate, β_2 microglobulin and microalbumin could not be used as these laboratory tests were not available during the time of the study. Acute kidney injury (AKI) could not be assessed because secondary data was used with creatinine clearance measurements having been done three to six months apart. The definition of nephropathy used in this study is neither exhaustive of all forms of nephropathy nor accurate. It only gives an indication of the burden. Kidney biopsies would have been more informative especially for HIVAN.

Due to the standard practice at the clinic where patients were screened for kidney function prior to initiation on TDF containing ART regimens, there is a channelling bias inherent in the cohort as far as the analysis of TDF as a risk factor because patients with compromised renal function were not initiated on the antiretroviral agent. There is also the likely misclassification bias due to the measurements used to define nephropathy as far as TDF toxicity is concerned. It would have been more appropriate to use biomarkers that directly measure tubular toxicity in addition to creatinine clearance.

None of the medications that were assessed were statistically significant as independent risk factors for nephropathy.

The study period spans across eras where different regimens were recommended as first line in Zimbabwe and used at Newlands Clinic. In the earlier part of 2007 to 2011, the alternative first line was predominantly used at the clinic which consisted of zidovudine/lamivudine/nevirapine [44]. The 2010 guidelines for antiretroviral therapy in Zimbabwe then introduced a different preferred first line regimen of tenofovir/lamivudine/nevirapine [18].

Although there are quality checks to ensure the data quality integrity, the data that was analysed was collected for operational purposes and not for research purposes. Clinicians collecting the data were not operating using standardised methods as in a research context, but the information collected was done as part of clinical care.

5. Conclusion

The incidence of nephropathy was low in this cohort. The traditional risk factors for renal disease including older age and diabetes mellitus emerged as significant independent risk factors. HIV wasting syndrome and history of pulmonary tuberculosis were also independent risk factors suggesting that advanced disease is probably a risk factor for the development of nephropathy. In order to detect, and prevent the development of nephropathy in HIV infected patients, it is important that ART should be started early, and ART care services should be complimented with proper diabetic care. Patients that develop pulmonary tuberculosis, HIV wasting syndrome or are initiated on ART above the age of 45 years should have regular assessments of renal function.

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