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Renal dysfunction in HIV-infected patients commencing antiretroviral therapy in a treatment centre in southern Nigeria

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Abstract
Objective: As HIV becomes a more manageable chronic condition, with increasing life expectancy and an ageing population, kidney disease due to HIV or antiretroviral therapy (ART) have become more prominent. Moreover, the nephrotoxic potential of some frontline antiretroviral drugs has become established. The study aimed to evaluate the prevalence and risk factors for renal dysfunction among HIV-infected patients commencing ART at a southern Nigerian tertiary hospital.
Methods: A cross-sectional prospective study involving 263 HIV-infected treatment-naïve patients commencing ART at the University of Port Harcourt Teaching Hospital, Port Harcourt. Blood and urine samples were taken from randomly recruited patients for appropriate laboratory analysis. The MDRD formulae were used for evaluating renal function while renal dysfunction was defined as an estimated glomerular filtration rate ≤ 60mls/min/1.73m^2 and /or proteinuria.
Results: The average age of enrolled patients was 36.3±10.15 with 59.3% women. 33.8% had proteinuria and 6.5% had eGFR<60mls/min/1.73m^2. The prevalence of renal dysfunction was 37.6%. Age > 50 years, anaemia and use of Traditional medicine were independent predictors of renal dysfunction.
Conclusion: In this cohort of treatment naïve HIV patients, a high prevalence of renal dysfunction exists. Older age, anaemia and traditional medicine use were predictors of renal dysfunction. There is a need for clinicians to monitor these variables, especially the use of Traditional medicine which is easily overlooked in practice.

Keywords: HIV, Renal dysfunction, Traditional medicine, Antiretroviral Therapy, Proteinuria

Plain English Summary

As HIV infection continues to remain a significant public health problem, death and ailments due to the disease are in decline due to the effectiveness of the drugs used in its management. However, diseases of chronic ailments including Kidney abnormalities have become more prominent in this population of patients. This is mainly because some of the frontline drugs including Tenofovir used in the treatment of HIV have been found to have the potential to cause kidney disease.
In this study, we seek to identify the prevalence of kidney disease in the population of HIV-infected patients starting treatment at a tertiary hospital in southern Nigeria. We also seek to know the factors associated with the development of kidney disease in these patients.

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We randomly recruited 263 HIV-infected patients yet to commence treatment. We collected urine and blood from them for laboratory analysis. We defined kidney disease as egfr≤60mls/min/1.73m^2 and /or the presence of dipstick proteinuria.
Of the 263 patients in the study, 59.3% of them were women and the average age was 36.30±10.15. 33.8% of patients had proteinuria while a total of 37.6% had kidney disease.
Older patients, those with anaemia and patients using traditional medicine were found to be more at risk of developing kidney disease in this population studied.
We concluded that in Nigerian HIV patients about to commence treatment, kidney disease is high and older patients, those with anaemia and patients using traditional medicine would need to be identified and monitored closely as they prepare to start treatment for HIV. This is especially important for those patients using traditional medicine since this aspect is usually neglected by clinicians during interactions with patients.

Introduction

Human immunodeficiency virus (HIV) continues to pose significant public health challenges around the world. Its burden is known to be heavier in sub-Saharan Africa compared to other regions of the world. This is made worse by a combination of factors including ignorance, high illiteracy levels and comorbid diseases. Nigeria has the third highest HIV/AIDS burden in the world with an estimated 1.9 million people living with the disease and 51000 deaths due to AIDS in 2021 (1). Despite this huge burden, a significant number of eligible children and adults are not accessing lifesaving antiretroviral drugs.

The use of antiretroviral therapy (ART) has changed the landscape of HIV/AIDS and reduced the disease to a manageable chronic ailment with reduced morbidity and mortality even in sub-Saharan Africa. However, the success story of ART brings with it an increased life expectancy and an ageing population of HIV-infected patients. Consequently, diseases of ageing including those of the kidneys and the cardiovascular system are gaining prominence in this population of patients. Moreover, with the increasing rollout of antiretroviral drugs in Africa, issues of efficacy and safety will play increasing roles in the drive for universal access to therapy.

By 1984, reports had emerged in the scientific literature associating kidney injury with HIV infection. Specific HIV-associated nephropathy (HIVAN) was defined as a distinct entity with known clinicopathologic features thought to be associated with the late stages of the disease (2). Kidney disorders are now known to be associated with all stages of HIV infection and range from acute kidney injury (AKI), to chronic kidney disease (CKD) and end-stage renal disease (ESRD) (3, 4). Improvements in kidney function in HIV-infected patients on combination antiretroviral therapy have been widely reported but infected individuals are still at a greater risk of chronic kidney disease than the general population and kidney function may continue to deteriorate despite the use of ART (3).

In patients starting therapy for HIV infection, a higher prevalence of renal dysfunction has been reported in different cohorts across sub-Saharan Africa (5, 6), and as in the general population, these patients with CKD have a higher risk of cardiovascular and all-cause mortality.

A disparity in the prevalence of CKD and response to combination ART exists between patients of African descent and HIV-infected Caucasians, while wide variations in the prevalence of kidney disease in patients commencing ART have been reported across countries and different regions of the same country (5, 7). Genetic and environmental factors may at least in part explain this variability. Furthermore, with a high prevalence of comorbidities including Hepatitis B, Hepatitis C, Diabetes Mellitus, cardiovascular diseases as well as cultural practices which may be at variance with what obtains in other climes, it is conceivable that the predictors of renal dysfunction among HIV-infected patients in this environment may be different.

Many antiretroviral drugs are eliminated by the kidneys and may require dose adjustment in patients with CKD. Nevertheless, some antiretroviral drugs including Tenofovir, a nucleotide reverse transcriptase inhibitor, have been associated with renal dysfunction in a wide spectrum of HIV-infected patients (8). Tenofovir is now an established first-line agent for the treatment of ART naïve HIV infected persons across Africa. With this development, pre-treatment screening for renal dysfunction is imperative.

We hypothesize that risk factors for renal dysfunction among HIV-infected patients commencing ART in this region may vary from those reported.

This study is therefore aimed at providing data on the prevalence and risk factors for renal dysfunction among Nigerian HIV-infected patients commencing antiretroviral therapy at the University

of Port Harcourt Teaching Hospital in South-South Nigeria.

Methods

This study is part of a wider study at the University of Port Harcourt Teaching Hospital (UPTH) aimed at evaluating renal safety and novel Biomarkers in Nigerian HIV-infected patients exposed to Tenofovir (the ERSABIN Study). This report is a prospective cross-sectional study carried out at the medical outpatient clinic of the hospital among ambulating HIV-infected patients presenting at the centre for evaluation and commencement of antiretroviral therapy. The UPTH is a tertiary hospital located in Port Harcourt, Rivers State, a coastal city and a major oil hub of the Niger Delta region of south-south Nigeria. The hospital serves as a major referral centre and a teaching hospital for undergraduate and postgraduate medical students and doctors of the University of Port Harcourt. It is also a major treatment centre for patients with HIV infection in the region.

Two hundred and sixty-three consecutive patients attending the HIV clinic for counselling and commencement of antiretroviral therapy who met the eligibility criteria and consented to participate in the study were recruited into the study. Patients who were at least 18 years of age, were treatment-naïve and were about to commence antiretroviral therapy were recruited. Patients who were unable to give informed consent, pregnant women, patients with diabetes, known renal disease, or tuberculosis (including those on aminoglycoside-based anti-TB regimen) were excluded from the study. All patients gave written informed consent after the study had been introduced to them and a patient information leaflet about the study was given to them. Time was given for proper consideration. After consenting to participate, a case review form containing questions on social and demographic information including those of age, gender, drug use history and use of traditional medicine was filled by all participants with the help of members of the study team. Traditional medicine for this study refers to all forms of complementary and alternative medicines including herbals.

Blood and freshly voided urine were collected from all study participants for laboratory investigations which included haemoglobin, urinalysis, Hepatitis B surface antigen, Hepatitis C antibody and CD4 cell count. All laboratory investigations were done at the hospital's central laboratory. Blood pressure, weight and height were measured using standard protocols. Proteinuria was measured by dipstick using combi 9(meditest combi 9 – Duren Germany). Renal function was determined by estimated glomerular filtration rate (eGFR) using the modified MDRD equation. Renal dysfunction was defined as an eGFRr< 60ml/min / 1.73m^2 and/ or the presence of proteinuria on dipstick urinalysis. Hypertension was defined as a systolic BP of ≥ 140mmHg and /or a diastolic BP of ≥ 90mmHg or the use of an antihypertensive drug. Anaemia was defined as a haemoglobin level of <10g/dl. Pulse pressure was calculated as the difference between the systolic and diastolic blood pressure values while wide pulse pressure is defined as pulse pressure ≥60mmHg. The study commenced only after approval had been given by the Research ethics committee of the University of Port Harcourt Teaching Hospital.

Data Analysis

Data analysis was done using SPSS version 20 (SPSS Inc, Chicago IL, USA). Descriptive statistics was used to express data as means ± standard deviation for quantitative data and percentages for qualitative data. Chi-square analysis and Fisher's exact test were used for categorical data to assess relationships between groups. Independent sample t-test was used to compare parametric data according to renal dysfunction status. Linear regression models (univariate and multivariate) were used to assess the relationship between pulse pressure and renal function as measured by eGFR. Various factors associated with renal dysfunction were explored. Variables that were <0.25 at the univariate analysis were included in the multivariate model. A backward stepwise logistic regression model was used to identify factors independently associated with renal dysfunction.

Results

Of the two hundred and sixty-three patients recruited into the study, 156(59.3%) were females. The mean age of the study population was 36.30±10.15 (range 18-72 years). Twenty-six per cent (26%) of the population were above 40 years of age. The prevalence of renal dysfunction in the study population was 37.6% (99 out of 263) while 17(6.5%) patients had eGFR <60. Dipstick proteinuria was seen in 89(33.8%) of the study population with women being in the majority of that subpopulation (62.9%). In the population of patients with renal dysfunction, only 35% were men. The mean age of patients with renal dysfunction was 37.71±11.21. However, 27(39.13%) of the patients over 40 years of age in the study had renal dysfunction. According to the Kidney Disease Outcomes Quality Initiative

(KDOQI), guidelines on kidney disease classification based on the GFR, 109(41.4%), 137(52.1%), and 17(6.5%) of the study population were in stages 1, 2 and 3 of renal disease (9). No patient in our study was in stage 4 or 5 kidney disease. The prevalence of hypertension in the study population was 17.9% while 4.2% of the population tested positive for Hepatitis B surface antigen. The mean pulse pressure values between the patients with renal dysfunction and those without renal dysfunction did not show a statistically significant difference. Over thirty percent (30.8%) of the study population had anaemia while nearly forty percent (39.9%) used traditional medicine. Although differences in trend were seen in the mean values of CD4, Systolic and Diastolic Blood pressures between patients with renal dysfunction and those without renal dysfunction, these differences did not reach statistical significance. However, statistically significant differences were seen in Body Mass Index (BMI), eGFR, anaemia and Traditional medicine use between the two groups of patients. Table 1 shows some demographic and clinical characteristics of the study population.

Table 1: Demographic and clinical characteristics of study participants

Variable	All	HIV subjects with renal dysfunction	HIV subjects without renal dysfunction	p-value
Age (years)	36.3±10.15	37.71±11.21	35.45±9.38	0.080
BMI	21.55±3.57	20.65±3.61	22.09±3.44	0.001
CD4 (cells/µl/m)	181±50	171.10±109.13	187.80±110.65	0.235
Haemoglobin	10.71±1.89	10.15±1.87	11.06±1.82	0.001
Systolic blood pressure	116.73±15.35	115.41±15.06	117.52±15.51	0.282
Diastolic Blood pressure	75.26±10.31	74.48±10.85	75.73±9.97	0.342
eGFR	87.17±19.65	84.13±22.10	89.04±17.80	0.049
Anaemia	81(30.8%)	43	38	0.001
Trad. Med. use	105(39.9%)	49(46.7%)	56(53.3%)	0.019
Pulse pressure	41.47±9.67	40.97±9.02	41.80±10.05	0.477

Factors associated with renal dysfunction were explored. Pulse pressure was also explored relative to eGFR values. A linear regression model established that pulse pressure could significantly predict eGFR, F= 6.826, P = 0.010 (unadjusted) and 0.033(adjusted) and pulse pressure accounted for 2,6% of the explained variability in eGFR with adjusted R^2 =2.2% though a small effect size according to Cohen (10). Figure 1 shows the relationship between pulse pressure and eGFR.

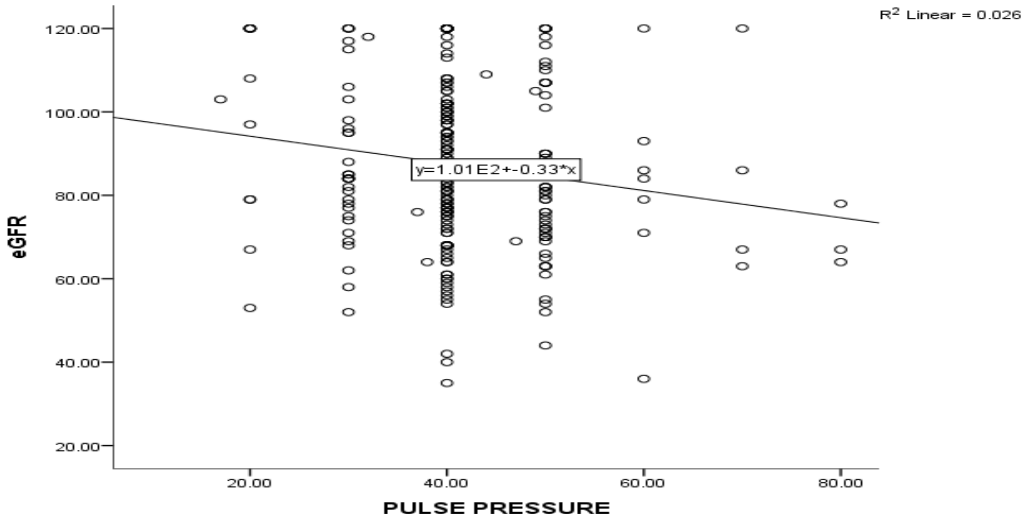

Figure 1: Correlation between Estimated Glomerular Filtration Rate (eGFR) and Pulse Press R= 0.160. P= 0.010

Table 2 shows the relationship between renal function as measured by eGFR and some important variables. In the linear regression model shown in Table 2, age and pulse pressure were significantly associated with renal function in both the univariate and multivariate analysis while CD4 cell count showed a trend in the multivariate linear regression model.

Table 2: Linear regression model for associations with renal function (eGFR)

Variable	Univariate			Multivariate		
	OR	CI	p-value	OR	CI	p-value
Age (years)	-0.498	-0.726, -0.270	0.001	-0.485	-0.715, -0.256	0.001
CD4 cell count (cells/µl/m)	0.015	-0.006, -0.037	0.164	0.020	-0.001, -0.041	0.060
BMI	-0.369	-0.139, -0.301	0.280			
Pulse pressure	-0.326	-0.571, -0.080	0.010	-0.393	-0.753, -0.032	0.033
Systolic Blood Pressure	-0.100	-0.256, -0.056	0.209	0.129	-0.097, -0.355	0.263

Table 3 shows the results of univariate and multivariate logistic regression analysis. Age>50, BMI < 18.5, use of Traditional medicines and anaemia were significantly associated with renal dysfunction in the univariate model of this cohort. However, Age > 50 years, use of Traditional medicine and anaemia remained significant predictors in the multivariate model.

Table 3: Logistic regression for predictors of renal dysfunction

Variable	Univariate			Multivariate		
	OR	CI	P-value	OR	CI	P-value
Age(years). >50years	0.40	0.187 - 0.825	**0.014**	2.50	1.150 – 5.444	**0.021**
CD4 <200 (cells/µl/m)	0.73	0.217 - 2.420	0.601			
BMI <18.5kg/m^2	2.22	1.207 - 4.097	**0.010**	1.63	0.835 -3.182	0.152
Anaemia	2.55	1.487 - 4.361	**0.001**	2.10	1.171 -3.778	**0.013**
Traditional medicine use	1.89	1.136 - 3.145	**0.014**	2.08	1.216 -3.554	**0.008**
Systolic Blood Pressure (mmHg)	0.99	0.974 - 1.008	0.282			
Diastolic Blood Pressure (mmHg)	0.99	0.964 - 1.013	0.341			
Wide Pulse Pressure	0.74	0.417 - 1.318	0.398			
Gender	1.43	0.855 - 2.394	0.172	0.85	0.487 -1.499	0.583

Figure 2 illustrates the relationship between traditional medicine use and renal function.

Figure 2: Relationship between Estimated Glomerular Filtration Rate (eGFR) and Use of Traditional medicine P= 0.001

Discussion

Our study examined renal dysfunction in a cohort of HIV-infected Nigerian patients initiating antiretroviral therapy. Renal dysfunction was defined as eGFR <60 and /or positive proteinuria on dipstick. In this study, we observed a high prevalence of renal dysfunction (37.6%) with a National Kidney Foundation's KDOQI class 3 (eGFR <60) or lower of 6.5%. We also observed a significantly higher risk of developing renal dysfunction in association with some traditional risk factors including age> 50 years, low BMI(BMI<18.5) and anaemia. Studies in Nigeria and other parts of Africa have reported a high prevalence of renal dysfunction among HIV-infected patients commencing ART (5, 11, 12). Our finding of 37.6% is in agreement with reports from Ile Ife (5) in South western Nigeria, but lower than reports from Kano (56.8%) in the Northwest (13) and Illorin (47%) in the North central region of Nigeria (14). In other parts of Africa, varying prevalences have also been reported. A study in Uganda reported a 20% prevalence (15), while a study from Tanzania reported a prevalence of 28.4% (16). This wide variation in the prevalence of renal dysfunction could in part be due to differences in study design, populations studied ie demography and ethnicity, as well as the definitions used for renal dysfunction.

While some studies used only dipstick proteinuria measurements, others quantified it, and yet others used creatinine ratios and GFR. Nevertheless, variable histological patterns reported by different workers across sub-Saharan Africa may lend credence to a high degree of genetic variability among patients from different cohorts. Nigeria has a multiplicity of ethnic groups and genetic influence on disease outcomes may manifest in multiple patterns even within the same region as seen in reports from northwestern Nigeria (13, 17). Indeed, studies have reported an association between multiple common single nucleotide polymorphisms (SNPs) in the MYH9 gene with a two to four times greater risk of non-diabetic end-stage renal disease and could account for the excess risk of CKD observed in Africans (18). Recent studies have shown stronger associations between SNPs in the APOL 1 gene and HIVAN (19).

In our study, 33.8% of all patients and 89% of patients with renal dysfunction had positive dipstick proteinuria. This is higher than was reported in some studies (3, 20) and lower than in others (21, 22). Proteinuria is a common occurrence in HIV-infected patients, is predictive of CKD progression in the general population and is associated with faster progression of HIV infection (23, 24). The women's inter-agency study demonstrated an association between proteinuria/elevated serum creatinine and an increased risk of death among HIV-infected women (25, 26). Proteinuria may be related to worsening outcomes due to increased systemic immune activation as a result of persistent inflammation, and increased infiltration of activated T cells in renal interstitium with consequent renal damage (27).

Age >50 years was found to be a predictor of renal dysfunction in this study. Indeed, older patients above 50 years of age were two and a half times more likely to develop renal dysfunction compared to younger patients. In the general population, it has long been known that renal function declines with age. This has also been shown in the HIV population by some studies (11, 28) while others have not found any association (16, 29).

Gender differences exist in the prevalence of renal dysfunction in this study though this difference did not reach statistical significance. Among patients with renal dysfunction, 65% were women. This is at variance with findings in some studies but agrees with those of others (5, 30). This difference may be environmental or due to some unexplored factors.

A non-statistically significant difference was also seen in the mean CD4 values between patients with renal dysfunction and those without. This is at variance with several studies (12, 16, 20) and may have been due to patient selection. Our patients were ambulatory and must have the capacity to give informed consent. However, a lower CD4 count in patients with renal dysfunction justifies observations that a decreased CD4 count could be a risk factor for kidney disease. More patients with renal dysfunction in our study had CD4 counts <200 cells/µl.

An exploration of associations between renal function and other important parameters of morbidity and mortality revealed a significant negative correlation between pulse pressure and renal function as measured by eGFR. Even as hypertension remains non-significantly associated with renal dysfunction, this observation of a significant correlation and predictor ability of pulse pressure in an adjusted linear regression model remains important. Pulse pressure as a blood pressure parameter is an important predictor of mortality (31). This inverse relationship between pulse pressure and eGFR remained in our multivariate linear regression model even after adjusting for possible confounders including Age, CD4, and Systolic blood pressure (P= 0.033) as seen in Table 2. Several studies have found an independent association between pulse pressure and adverse renal outcomes in the general

population (32, 33). Pulse pressure is a reflection of arterial stiffness and may be an independent risk factor for the progression of CKD. In the RENAAL trial, after controlling for multiple potential confounders, a10mmHg higher pulse pressure was significantly associated with a 17% higher relative risk of developing ESRD. Furthermore, among 329 patients with CKD(mean eGFR of 39ml/min per 1.73m^2,), a 10mmHg higher pulse pressure was significantly associated with a 10% greater relative risk of kidney function decline after six months of follow-up (34, 35). Pulse pressure has also been reported to be independently associated with urine protein excretion (36). In HIV-infected treatment-naïve patients, Pulse wave velocity, a measure of arterial stiffness, has been demonstrated to be increased (37). In light of an ageing HIV population, greater attention needs to be directed at this relationship.

Our study showed anaemia as a strong independent predictor of renal dysfunction. This association has also been reported by previous studies (5, 28, 30, 31). Anaemia is considered to be a marker of disease progression in patients with HIV and a predictor of increased mortality. In HIV-infected patients, declining haemoglobin could be due to several factors including a decrease in the lifespan of erythrocytes, decreased erythropoietin production and changes in iron homeostasis. In HIV patients with CKD, decreased quality of life, poor cognitive function and increased mortality have been reported. HIV infection and renal dysfunction have also been reported to have a combined impact on decreasing hemoglobin levels thus increasing the risk of anaemia (38).

Body Mass Index (BMI) was found to be associated with renal dysfunction in this study at the univariate level. Patients with BMI <18.5 were more likely to develop renal dysfunction compared to those with higher values of BMI although the association was not significant in the adjusted model. Moreover, Table 1 showed that patients with renal dysfunction had significantly lower BMI than those without renal dysfunction (P = 0.001 on independent t-test) Previous studies have reported an association between low BMI and CKD (13, 20, 28). This strengthens the case for good nutrition in maintaining optimal health and delaying disease progression in patients with HIV.

In our study, a nontraditional factor, the use of Traditional medicine, was found to be an independent predictor of renal dysfunction. In this study, the risk of developing renal dysfunction among HIV patients commencing therapy was twice as much in those who used traditional medicine compared to those who did not (OR 2.08; P=0.008). while traditional medicine is commonly used by HIV-infected patients, its effect on renal function in this population has not been well defined in this environment. The WHO estimates that 80% of the world's population complements conventional therapy with traditional folk medicines in some aspects of their healthcare (39). In Africa, herbal medicines are often used as primary treatment for HIV and for HIV-related problems with many patients taking a broad range of natural health products in addition to their conventional drugs. This is done without clear clinical evidence of efficacy and the possibility of toxicity. In our study, 39.9% of patients used traditional medicine. Studies have shown a high prevalence of the use of traditional medicine among HIV-infected patients (40, 41). Traditional medicines are easily accessible, and inexpensive and are believed by consumers to be safe and harmless. However, contrary to these beliefs, studies have demonstrated the importance of traditional medicines as a cause of renal disease in the general population (42). The kidneys are particularly vulnerable to toxic injury, and as the renal tubules are involved in active transport and urinary concentration, a high concentration of these toxins from traditional medicine could cause direct injury to the tubular cells. Indeed, adulteration of herbal medicines is common. Furthermore, traditional medicines can interact with conventional medicines. As HIV-infected patients use antiretroviral drugs with concomitant use of traditional herbal medicines, issues of drug-drug interactions, herb-drug interactions, and herb-herb interactions as well as genetic polymorphisms in genes coding for drug-metabolizing enzymes may become important. Host genetic factors play key roles in the efficacy and toxicity of ART and by extension, those of traditional medicines. With a high genetic diversity, Nigerian HIV patients would conceivably be susceptible to the impact of polymorphisms in drug metabolizing enzymes and transporters on drug disposition. Polymorphisms in genes coding various transporters involved in the disposition of the nephrotoxic antiretroviral drug Tenofovir are established (43). It is conceivable that the same drug-metabolizing enzymes and transporters involved in the disposition of conventional drugs are also involved in the disposition of herbal traditional medicines. In a highly genetically diverse region such as Nigeria, the implication of the interactions arising from concomitant use of traditional medicines and combination antiretroviral drugs including Tenofovir could be far-reaching. Data relating SNPs in specific genes associated with renal

dysfunction and drug levels in patients on ART and concomitant herbal medicines could give an insight into the mechanism of renal dysfunction seen in HIV-infected patients using traditional medicines.

Conclusion

This study showed a high prevalence of renal dysfunction in HIV-infected patients commencing antiretroviral therapy in South-South Nigeria. Age > 50 years, Pulse pressure, anaemia and use of Traditional medicine were found to be predictors of renal dysfunction while Low BMI remained in association. With expanding access to ART and the wider use of some nephrotoxic drugs including Tenofovir as first-line agents, these predictor variables need to be carefully monitored especially in regions with high genetic variability. Early screening for markers of renal dysfunction, and emphasis on drug use history including those of traditional medicine should play important roles in the management of HIV. Research into the mechanistic relationship between traditional medicines and renal dysfunction should be encouraged.

List of Abbreviations

AKI: Acute kidney injury
ART: Antiretroviral therapy
BMI: Body mass index
CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate
ESRD: End-stage renal disease
HIV: Human immunodeficiency virus
HIVAN: HIV-associated nephropathy
KDOQI: Kidney Disease Outcome Qualitative Initiative
MDRD: Modification of diet in renal disease
PP: Pulse pressure
SNP: Single nucleotide polymorphisms
TB: Tuberculosis

Declarations

Ethics approval and consent to participate

Before the commencement of the study, the University of Port Harcourt ethics committee gave written approval (UPTH/ADM/90/S.11/VOL X/285). All study participants were given patient information leaflets describing every aspect of the study including the reason for the study. Only patients who gave written consent for the study were recruited into the study. Confidentiality of patient information was guaranteed by ensuring that study participants were identified by study ID numbers and information collected from study participants was used only for the study.

Consent for Publication:

All the authors gave their consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license. Otherwise, all copyright ownership including all rights incidental thereto are conveyed to the journal when published

Availability of data and materials

The study data is available upon request to the corresponding author.

Competing interests

The authors declare that no competing interests exist.

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Authors' contributions

TI was responsible for the concept, design, data collection, data analysis, manuscript draft and revision. EP was responsible for data collection, data analysis, manuscript draft and revision. TIT was responsible for data collection, manuscript editing and revision. All the authors approved the final version of the manuscript.

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