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Prevalence and correlates of chronic kidney disease (CKD) among ART-naive HIV patients in the Niger-Delta region of Nigeria

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Abstract

Widespread use of antiretroviral therapy (ART) in human immunodeficiency virus (HIV) patients has led to improved longevity with the attendant increase in noncommunicable disease prevalence including chronic kidney disease (CKD). This study documents the prevalence of CKD in a large HIV population in Southern Nigeria.

This is a single center, 15-year analysis in ART-naïve patients. CKD was defined as the occurrence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 on 2 consecutive occasions 3 to 12 months apart using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation. The Cochran-Armitage and Cuzick tests were employed to assess for trend across the years for CKD prevalence and CD4 count, respectively. Multivariable logistic regression models were used to identify independent associations with CKD.

In all, 1317 patients (62.2% females) with mean age of 34.5 years and median CD4 count of 194 cells/μL were included. CKD prevalence was 13.4% (95%CI 11.6%–15.4%) using the CKD-EPI equation (without the race factor). Multivariable analysis identified increasing age and CD4 count <200 cells/μL as being independently associated with CKD occurrence.

This study reports a high prevalence of CKD in ART-naïve HIV-infected patients. Measures to improve diagnosis of kidney disease and ensure early initiation of treatment should be integrated in HIV treatment programmes in this setting.

Abbreviations: APOL = apolipoprotein, ART = antiretroviral therapy, BMI = body mass index, CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HIV = human immunodeficiency virus, HIVAN = HIV associated nephropathy, SSA = Sub-Saharan Africa.

Keywords: CKD, HIV, Nigeria, prevalence

1. Introduction

As at the end of 2015, about 36.7 million people were living with the human immunodeficiency virus (HIV) globally with 23.5 million living in Sub-Saharan Africa (SSA).[1] Of those affected, 3.2 million individuals live in Nigeria with the highest prevalence reported from the Niger-Delta region.[2] Nigeria is estimated to have the 2nd highest HIV population in the world, with South Africa ranking 1st with 7 million affected individuals.[3] The increased availability of antiretroviral therapies (ARTs) in many SSA countries has led to increased life expectancy with an attendant increase of noncommunicable diseases among HIV populations.[1,4]

Kidney disease is a common complication of HIV infection[5,6] and HIV is a common cause of chronic kidney disease (CKD) in SSA.[7,8] Despite the rationing of dialysis in South Africa where being HIV positive adversely impacts on patients' chances of acceptance to dialysis, the South African Renal registry has recently reported an increase from 8.3% in 2012 to 9.3% in 2014 of HIV positive end-stage renal disease patients receiving dialysis.[9] One study from the US showed that the annual number of patients with incident end-stage renal disease secondary to HIV-associated nephropathy (HIVAN) increased steadily from 1989 to 1995 and then remained stable until 2006.[10] Also, some studies in Nigeria have documented high prevalence of kidney disease among HIV patients ranging from 22.9% to 51.8% depending on the geographic location and definition of kidney disease utilized.[11–14] Such data continue to highlight the impact of HIV on kidney disease. However, most of the studies have been underpowered and may therefore not report accurate estimates of CKD prevalence. There is therefore a need to assess kidney disease prevalence in SSA using a large HIV study

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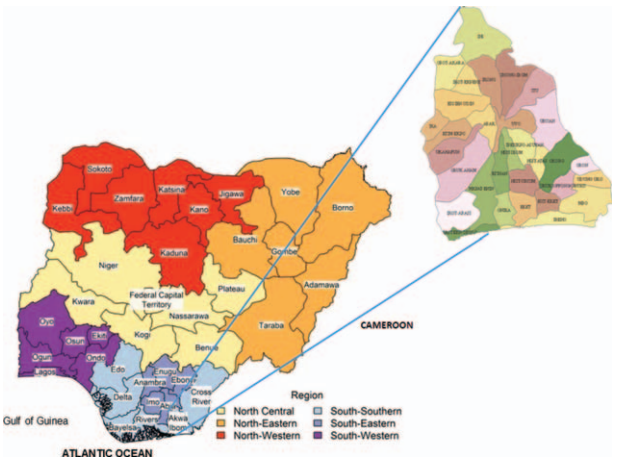

Figure 1. Map of Nigeria showing Akwa Ibom State.

population to provide a more accurate estimate of the disease burden. This will assist the planning for health services delivery in the region.

2. Methods

This study is a 15-year (2002–2016) assessment of renal function in ART-naïve HIV-infected patients at the University of Uyo Teaching Hospital (UUTH), Uyo, Nigeria (Human Research Ethics number: UUTH/AD/S/vol. XIX/15. August 9, 2016). The UUTH is the only tertiary health facility serving a population of over 4 million people in the extreme Southern (Niger-Delta) region of Nigeria (Fig. 1). The UUTH HIV clinic, funded by the United States Agency for International Development, is involved in voluntary counseling and testing for HIV, provision of ART, identification and treatment of opportunistic infections, and follow-up care for HIV positive patients. Clinical and demographic features such as age, gender, weight, height, body mass index (BMI), blood pressure, hypertension and diabetes mellitus (DM) status, and date of commencement of ART were extracted from the records. Records for CD4 count, viral load, electrolytes, urea, creatinine (measured using an isotope dilution mass spectrophotometry-traceable Jaffe kinetic reaction), hepatitis B surface antigen, and antibody to hepatitis C virus were also extracted. Serum creatinine is routinely done at first contact with the patient but programmatic deficiencies do not often allow repeat serum creatinine except in those who can afford out-of-pocket payment for the test. Information on proteinuria (dipstick assessment) was also recorded where available, because this was not routinely done. Hypertension was defined as 2 or more recordings of blood pressure with systolic blood pressure (SBP) at least 140 mm Hg and/or diastolic blood pressure (DBP) of at least 90 mm Hg or patients on antihypertensive medication.[15] Mean arterial blood pressure was calculated as [DBP + (SBP − DBP)/3]. DM was defined as fasting plasma glucose of at least 7.0 mmol/L and/or random/2 hour postmeal plasma glucose of at least 11.1 mmol/L[16] or in patients taking antidiabetic agents. Obesity was defined as BMI of at least 30 kg/m^2 in a patient without peripheral edema[17]; overweight as BMI of 25 to 29.9 kg/m^2 while BMI of 18.0 to 24.9 and less than 18.0 kg/m^2 were defined as normal and underweight, respectively. Dyslipidemia was defined using the National Cholesterol Education program adult treatment panel III criteria[18] – total cholesterol greater than 200 mg/dL or low density lipoprotein cholesterol greater than 150 mg/dL or high density lipoprotein cholesterol less than 40 mg/dL or triglycerides greater than 150 mg/dL.

For the purposes of this study, data were extracted from patient's physical case records and transferred into STATA 14 (StataCorp, TX) for analysis. The Student t test (or its nonparametric equivalent, the Mann–Whitney U test, where necessary) was used to compare continuous variables while the Chi-square test was used to compare categorical variables. CKD was defined as 2 consecutive values of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 recorded within 3 to 12 months apart. We estimated GFR using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.[19] The CKD-EPI equation without the race factor was utilized for estimating GFR in this study given that recent studies[20–22] have suggested that the inclusion of race may generate less precise estimates in SSA. Participants' kidney function was staged using the Kidney Disease outcome quality initiative classification.[23] The prevalence (and 95% confidence interval) of CKD in the overall population and subgroups among the HIV patients was computed. To increase the power to generate stable estimates over time, the entire time of observation was divided into 5 time periods of 3 years each. The Cochran-Armitage trend test was used to assess for the presence of linear trends in CKD prevalence while the Cuzick trend test was used to determine linear trend in median CD4 count over the study period. Multivariable logistic regression models (using a threshold significance of P-value <.25 in univariable analyses and known CKD risk factors) were used to identify independent predictors of CKD in the study population. Three sets of sensitivity analyses were performed using eGFR estimates with the race factor for the CKD-EPI equation; eGFR estimates using the 4-variable Modification of Diet in Renal Disease equation with and without the race factor; and eGFR estimates using the CKD-EPI equation without the race factor for the population with at least 1 serum creatinine record.

3. Results

3.1. Demographic and clinical features

A total of 6676 patients had at least 1 GFR estimate. Of these, 1317 had 2 GFR estimates performed 3 or more months apart.

Table 1 summarizes the demographic and clinical characteristics of included patients. From the sample of 1317 patients, 62.2% were female. The mean age at enrolment was 35.4 ± 9.5 years; median CD4 count was 194 (interquartile range 95–343) cells/μL; and 51.1% had CD4 count lower than 200 cells/μL. Hypertension was present in 43.6% (95% CI: 41.5%–49.9%) and DM in 8.8% (95% CI: 5.6%–12.9%). Obesity (BMI > 30 kg/m^2) was seen in 8.3% (95% CI: 6.7%–10.1%) of the study population, and overweight (BMI 25.0–29.9 kg/m^2) in 21.9%. Dyslipidemia was present in 28.8% (95% CI 26.3%–38.8%), hepatitis B in 5.7%, and hepatitis C infection in 2.2%.

3.2. Prevalence of CKD

Of the 1317 patients who had at least 2 creatinine measures (at initiation of care and 3 months or more apart), the prevalence of CKD using the CKD-EPI equation without race was 13.4% (95% CI: 11.6%–15.4%). There was no significant change in CKD prevalence between 2002 and 2016, P = .62 (Fig. 2) while the median CD4 count at presentation progressively increased over the same period (P = .01).

Table 1

Demographic and clinical characteristics of HIV positive patients with at least 2 measurements of glomerular filtration rate.

Variable	Value (N = 1317)
Age, years	35.4 ± 9.5
Female sex	819 (62.2)
Systolic BP, mm Hg	122.5 ± 24.8
Diastolic BP, mm Hg	79.9 ± 18.2
Mean arterial blood pressure, mm Hg	92.2 ± 17.2
Hypertension (n = 565)	258 (45.7)
Fasting plasma glucose, mmol/L	4.8 ± 2.2
Diabetes mellitus (n = 251)	22 (8.8)
BMI, kg/m^2 (n = 1081)	23.3 ± 4.5
Underweight	113 (10.5)
Normal BMI	641 (59.3)
Overweight	237 (21.9)
Obese	90 [8.3% (95% CI 6.7%–10.1%)]
Hemoglobin, g/dL	11.3 ± 2.2
Hepatitis C infection (n = 497)	17 [3.4% (95% CI 2.0%–5.2%)]
Hepatitis B infection (n = 829)	58 [7.0% (95% CI 5.3%–8.9%)]
Serum albumin, g/dL	39.0 ± 11.4
CD4 count, cells/μL	194 (95–343)
CD4 count (<200) (n = 1237)	632 (51.1)
CD4 count (<350)	939 (75.9)
Log viral load (n = 586)	3.9 ± 1.2
Total cholesterol, mg/dL (n = 783)	166.2 ± 54.1
Triglyceride, mg/dL	141.7 ± 70.9
LDL-c, mmol/L	85.1 ± 42.5
HDL-c, mmol/L	50.3 ± 30.9
Dyslipidemia (n = 232)	75 (32.3)
Dipstick proteinuria (yes) (n = 32)	18 (56.3)

BMI = body mass index, BP = blood pressure, CD4 = cluster of differentiation 4, CI = confidence interval, HDL-c = high density lipoprotein cholesterol, HIV = human immunodeficiency virus, LDL-c = low density lipoprotein cholesterol.

The prevalence of CKD (stages 3, 4, and 5) was 8.8%, 2.2%, and 2.4%, respectively. There was no significant gender difference in the CKD prevalence (male vs female prevalence of 7.8% vs 9.4% for stage 3; 2.0% vs 2.3% for stage 4; and 2.6% vs 2.3% for stage 5, $P = .75$). Those with advanced CKD (stages 4 and 5) constituted 4.6% of the total population.

3.3. Sensitivity analyses of GFR equation estimates

Using the CKD-EPI equation with the race factor, the prevalence of CKD was 8.9% (95% CI: 7.5%–10.6%). The proportion of patients with stages 3, 4, and 5 CKD was 4.9%, 1.9%, and 2.1%, respectively. The prevalence of advanced CKD (stages 4 and 5) was 4.0% for CKD-EPI equation (with race factor).

The modification of diet in renal disease equation without the race factor yielded a CKD prevalence of 15.9% (95% CI: 13.9%–17.9%) with stages 3, 4, and 5 constituting 11.1%, 2.4%, and 2.4%, respectively. With the race factor, stages 3, 4, and 5 accounted for 5.5%, 1.9%, and 1.97%, respectively, making up 9.3% of the study population.

Using the single eGFR at initiation of care, a CKD prevalence of 26.6% (95% CI 25.6%–27.7%) with stages 3, 4, and 5 being 20.3%, 3.1%, and 3.2%, respectively, using the CKD-EPI equation without the race factor. Using the CKD-EPI equation with the race factor, stages 3, 4, and 5 had prevalence of 12.9%, 2.5%, and 2.9% respectively summing up to a CKD prevalence of 18.3%.

3.4. Factors associated with CKD

On multivariable analysis, increasing age was associated with increased risk of developing CKD – odds ratio (OR) 1.07 (95% CI: 1.05–1.10; $P < .001$) (Table 2). HIV patients with CD4 count less than 200 cells/μL were also at increased risk of developing CKD (Table 2). The presence of DM, hepatitis B and C coinfection, and hypertension did not increase CKD risk at the multivariable level. Comparison of sociodemographic and clinical characteristics of those with 1 and 2 GFR estimates (Supplementary Table 1, http://links.lww.com/MD/C194) showed statistical (but not clinically relevant) difference in age; higher proportion of hypertension and DM among those with 2 GFR estimates and similar BMI, hemoglobin, and hepatitis B coinfection prevalence.

4. Discussion

This study is one of the few attempts, in a large HIV population in SSA, to report the prevalence of CKD at initiation of care. The main findings and therefore importance of this study are: showing a high prevalence of CKD in a population of HIV positive patients; identification of increasing age and low CD4 count as independent CKD risk factors in our HIV population.

The prevalence of CKD in our population of HIV positive patients is high. Several studies among HIV patients in Southern Nigeria[11,12,24,25] with similar sociodemographic characteristics have also shown high prevalence of HIV individuals with

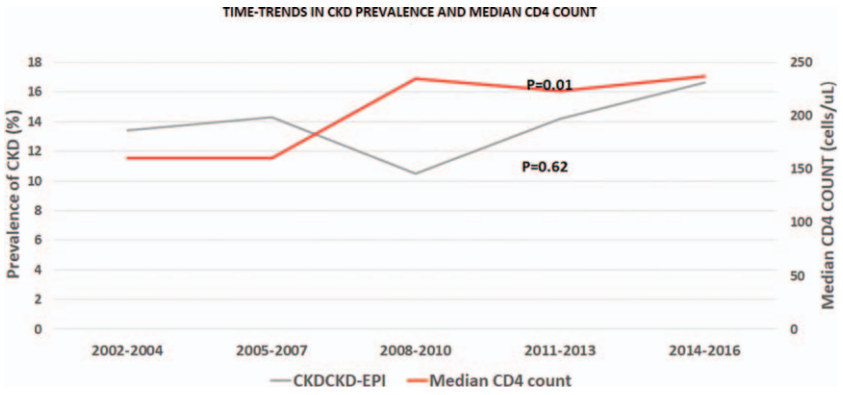

Figure 2. Relationship between CKD prevalence and median CD4 count (2002–2016). CD4 = cluster of differentiation 4, CKD = chronic kidney disease.

Table 2

Multivariate analysis of the predictors of CKD in HIV positive patients in the Niger-Delta region of Southern Nigeria.

	Univariable Odds ratio (95%CI) *P*-value	Multivariable Odds ratio (95%CI) *P*-value
Age, y	1.06 (1.04–1.08) **<.001**	1.07 (1.05–1.10) **<.001**
Female gender	1.15 (0.82–1.60) .41	1.44 (0.94–2.20) .09
CD4 count		
≥200 cells/μL	1	1
<200 cells/μL	1.65 (1.17–2.31) **.004**	1.51 (1.00–2.29) **.04**
Hypertension	1.68 (1.05–2.68) **.03**	1.72 (0.95–3.11) .07
Diabetes mellitus	1.74 (0.54–5.52) .35	2.68 (0.59–12.10) .20
BMI, kg/m^2	0.97 (0.93–1.02) .22	0.97 (0.93–1.02) .27
Positive hepatitis B	0.56 (0.22–1.43) .23	0.64 (0.21–1.91) .43
Positive hepatitis C	0.77 (0.17–3.43) .73	1.46 (0.29–7.39) .65
Time period		
2002–2004	1	1
2005–2007	1.08 (0.64–1.82) .78	1.05 (0.50–2.18) .94
2008–2010	0.76 (0.43–1.32) .33	0.47 (0.22–1.02) .06
2011–2013	1.07 (0.63–1.80) .80	0.97 (0.50–1.92) .95
2014–2016	1.29 (0.67–2.48) .44	1.13 (0.48–2.63) .78
Area under ROC*		**0.70**

BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, ROC = receiver operator characteristic.
* ROC curve of final multivariate logistic regression model.

eGFR < 60 mL/min/1.73 m^2 in ART-naïve patients. Some have reported prevalence as high as 47.6%[12] to 53%[24] when proteinuria was also considered, even though persistent proteinuria was not demonstrated in those studies and single eGFR measures were used which cannot discriminate between CKD and AKI patients. Other studies have equally reported a high prevalence of CKD among ART-naïve individuals in the West African sub-region such as Ghana (38.8%)[26] and Cameroon (54%).[27] In other African regions, the prevalence of CKD in HIV positive patients is variable with South Africa recording 2%[28,29] and Kenya 12%.[30] Overall, it has been shown that blacks (in SSA or other parts of the world) have higher risk of CKD when they are HIV-infected.[31]

A number of factors complicate the HIV-CKD interplay in Africa. First is the suboptimal implementation of available guidelines[32] for the screening, diagnosis, and management of CKD in HIV populations, especially in Africa. In our study population, less than 2% had dipstick proteinuria performed at initiation of care and none had proteinuria quantified either by spot or 24-hour urine collection. A recent report of the Global Kidney Health Atlas exploring global access of patients to health technologies and medications corroborates our finding by showing that African countries, of all world regions, had the lowest capacity for identification, monitoring, and management of CKD.[33] Secondly, there is a need to develop CKD risk assessment tools that aid the identification of high risk HIV patients for screening and initiation of appropriate therapies. Of the few available CKD risk assessment tools, one was derived from a predominantly Caucasian HIV population which differs significantly according to demographics from the HIV populations in SSA.[34] This tool has also not been validated in SSA HIV populations. Thirdly, GFR estimation formulae have not been properly validated in the HIV population. The few studies that have attempted doing this[35,36] either had very small sample sizes or were performed in a restricted population, making the results not generalizable. This leaves room for inconsistencies and great variations in the diagnosis of CKD among HIV-infected individuals. Recently, some workers in West Africa[20] have proposed the use of the full age spectrum serum creatinine-based equations constructed and validated by Pottel et al[37] in Caucasian populations. The best creatinine-based eGFR equation is yet to be determined for the African HIV population and considerable variations exist in the proportion of CKD among the HIV population depending on the equation used.

Late presentation of patients to the HIV clinics may also have contributed to the high prevalence of CKD in our study population. Many patients do not routinely go to hospital for treatment in Nigeria due to the cost (out-of-pocket payment) associated with health care. In this study, late presentation is supported by the relatively low CD4 counts of these patients at time of their first visit. A low CD4 count has also been documented as a risk factor for CKD in other HIV populations[38,39] probably mirroring more severe HIV disease, longer duration of exposure to HIV or presence of opportunistic infections all of which may predispose to both AKI and CKD. Increasing age and low CD4 counts were independent predictors of occurrence of CKD. Increasing age is a known risk factor for CKD in the general population and in the HIV population.[39] Recurrent diarrheal disease in HIV patients not having adequate care may also lead to repeated episodes of undiagnosed acute kidney injury which may ultimately lead to CKD. Other cultural factors like use of herbal remedies with unproven efficacy for HIV cure but with known nephrotoxic potential may also contribute to the increased CKD occurrence in HIV patients in West Africa. These factors were however not assessed by this study.

Although our study did not assess genetic factors, the increased prevalence of CKD in people of West African descent with HIV compared to other parts of the world may suggest a genetic predisposition.[40] Studies have reported that the presence of G1 and G2 high risk alleles of the apolipoprotein (APOL)1 gene is associated with HIVAN in South Africa.[41,42] High risk alleles of APOL1 have been documented as risk factors among nondiabetic CKD patients in South East Nigeria,[43] including a small group of HIVAN patients. Individuals with both APOL1 risk alleles have an estimated 4% lifetime risk for developing focal segmental glomerulosclerosis (FSGS), and untreated HIV-infected individuals have a 50% risk for developing HIVAN.[44] On the other hand, HIV positive patients without the risk variants have negligible risk of developing HIVAN as documented in the Ethiopian population.[45] A gene–environment interaction mediated by interferons and other cytokines (elaborated by the HIV infection) has been suggested as one of the factors leading to high CKD risk.[46] There is also the possibility of gene–gene interactions increasing the risk of CKD progression in HIV patients of West African origin suggesting the need for investigation of other genetic risk factors for CKD progression among HIV patients.

The large proportion of patients for whom urine protein was not assessed nor serum creatinine repeated suggests significant gaps in both the evaluation and care offered to HIV patients. It may be necessary to set up prospective studies in a more controlled setting to evaluate the real estimates of chronic kidney dysfunction.

Most of the patients with CKD in our study population were in stage 3 disease where there is still a window of opportunity to slow down or stop progression to end-stage kidney disease by early initiation of ART and other renal-specific interventions such as the use of ACE-inhibitors (or angiotensin receptor blockers) to reduce proteinuria and control of blood pressure. Early detection

and retarding of CKD progression through initiation of appropriate therapies may be more cost effective at retarding mortality given that access to treatment of advanced CKD is limited and expensive.[47]

4.1. Limitations

A limitation of this study includes the retrospective design as medical records of some patients who were registered at the HIV clinic were unavailable for assessment and inclusion into this study. However, given the large sample size of our study, we believe patients included are an adequate representation of the enrolled patients. Another study limitation relates to the unavailability of albuminuria. Our definition of CKD therefore depended only on serum creatinine and eGFR which could underestimate CKD prevalence. Studies reporting CKD prevalence using eGFR and albuminuria[5,6] generally tend to have higher prevalence rates than if CKD was diagnosed with eGFR only. This study is however strengthened by the large sample size and by utilizing various GFR estimation equations for assessing CKD. The large sample size increases confidence in the reported prevalence rates. The inclusion of patients across many years of activities has provided the opportunity of assessing the time trends.

5. Conclusion

This study reports a high prevalence of CKD in HIV positive patients in Nigeria. Earlier presentation of patients and earlier initiation of treatment could contribute to further reduction in the prevalence of disease. Strategies toward earlier identification of HIV positive patients at risk of CKD are therefore needed to reduce CKD burden among HIV patients in SSA. It is also important to determine the best serum creatinine-based GFR estimating equation for HIV patients in SSA.

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