Incidence and predictors of tenofovir disoproxil fumarate-induced renal impairment in HIV infected Nigerian patients

Bazim V. Ojeh[1,], Isaac O. Abah[2], Placid Ugoagwu[3], Patricia A. Agaba[4], Oche O. Agbaji[5], Steven S. Gyang[6]*

Abstract

Introduction **The use of tenofovir disoproxil fumarate (TDF) in the treatment of HIV infection has been associated with renal dysfunction. In Nigeria, data on the incidence and risk factors of TDF nephrotoxicity is sparse. We determined the cumulative incidence of and risk factors for TDF-induced renal impairment in HIV-infected individuals accessing care at the antiretroviral therapy (ART) clinic of Jos University Teaching Hospital, Nigeria.**

Methods **This retrospective cohort analysis included patients aged ≥16 years that initiated ART between January 2008 and December 2011. Renal impairment, defined as glomerular filtration rate GFR <60 mL/min/1.73 sqm using the Modification of Diet in Renal Disease (MDRD) equation was assessed at baseline and at 48 weeks on ART. Logistic regression was performed to determine factors associated with incident renal impairment.**

Results **The mean age was 39±9 years, and 67.1% were female. The cumulative incidence of renal impairment among the TDF-exposed and TDF-unexposed groups was 4.6% and 2.3% respectively (p<0.001). TDF exposure was significantly associated with renal impairment [OR=2.0, 95%CI=(1.48-2.89), p<0.001] in bivariate analysis. In multivariate analysis, older age (aOR=1.06, 95%CI=(1.05-1.08), p<0.001), TDF exposure [aOR=1.85, 95%CI=(1.31-2.60), p<0.001] and co-morbidities [aOR=2.71, 95%CI=(1.72-4.25), p<0.001] were significantly associated with renal impairment.**

Conclusion **TDF exposure, aging and comorbidities were predictors of renal toxicity among HIV positive patients. Regular monitoring of renal function in such high-risk individuals is recommended.**

Keywords **Renal impairment, TDF, nephrotoxicity, antiretroviral agents**

Introduction

Since its approval by the US Food Drug and Administration in 2001,[1] tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor, has enjoyed a global acceptance as a component of both first line and second line antiretroviral regimens due to its efficacy,[2] low incidence of adverse events,[2,3] convenient pharmacokinetic profile[4] and positive clinical outcomes.[2] Despite its proven efficacy, routine clinical use of TDF has been associated with significant risk of kidney tubular dysfunction,[5] which can manifest as Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, acute and chronic kidney injury.[1,6,7] Bone disease following TDF use has also been reported.[8] Cooper et al. conducted a systematic review and meta-analysis of 17 studies with a median sample size of 517 HIV-infected participants and reported a moderate but

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[1]Bpharm, MSc, AIDS Prevention Initiative in Nigeria (APIN), Jos University Teaching Hospital, P.M.B 2076 Jos, Nigeria; [2]BPharm, MSc, MPH, Pharmacy Department, Jos University Teaching Hospital, P.M.B 2076 Jos, Nigeria; [3]BSc, AIDS Prevention Initiative in Nigeria (APIN), Jos University Teaching Hospital, P.M.B 2076 Jos, Nigeria; [4]BmBcH, FWACP, Department of Family Medicine, University of Jos, P.M.B 2084 Jos, Nigeria; [5]MBBS, FMCP, Department of Medicine, University of Jos, Jos University Teaching Hospital, P.M.B 2076 Jos, Nigeria; [6]Bpharm, MSc, PhD, Department of Pharmacology, University of Jos. P.M.B 2084 Jos, Nigeria.

*Corresponding author: Bazim V. Ojeh, Bpharm, MSc, AIDS Prevention Initiative in Nigeria (APIN), Jos University Teaching Hospital, Jos, Nigeria. bazimojeh@gmail.com

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significant decline in renal function in the TDF-exposed group relative to the control.[5] The incidence of TDF-related nephropathy appears to be on the increase as seen in a recent cohort study of 440 patients initiated on TDF-based regimen which reported an incidence of 12%.[9]

Risk factors previously reported to be associated with TDF-induced nephropathy include older age,[10-13] TDF exposure[14,15] comorbid conditions such as diabetes, hypertension,[10,16] underweight,[10,12] baseline CD4 <200 cells/cmm,[10,12] female gender,[12,13,17] co-infection with hepatitis C virus (HCV),[14,17] hepatitis B virus (HBV),[18] concurrent use of nephrotoxic drugs,[19] and treatment with ritonavir-boosted protease inhibitors.[12,17,20]

In Nigeria, large numbers of HIV infected individuals are being initiated on a TDF-containing regimen in keeping with the recommendations by WHO.[21] However, data on the incidence and predisposing risk factors of TDF-induced renal dysfunction is sparse in Nigeria. Such information, therefore, would raise awareness to the burden of TDF-related kidney toxicity and can be used to develop interventions in line with best clinical practice. This study set out to determine the incidence and predictors of TDF-induced nephropathy in HIV-1 infected patients at the HIV clinic of the Jos University Teaching Hospital (JUTH) in Jos, Nigeria.

Methods

Study design

This was a retrospective cohort study of patients initiated on antiretroviral therapy between January 2008 and December 2011. At the time of this study, the eligibility criteria for initiation of antiretroviral therapy were based on the Nigerian national adult ART treatment protocol which recommended antiretroviral drugs for all HIV-infected adults with CD4 cell count <350 cells/cmm or those with opportunistic infections classified as WHO clinical stage 3 or 4. Following ART initiation, patients received monthly ART. Depending on whether the antiretroviral regimen contained TDF or not, patients were grouped as TDF-exposed and TDF-unexposed. Laboratory investigations such as CD4 cell count, HIV-1 RNA viral load, full blood count, and blood chemistry were done at 12 weeks and subsequently every 24 weeks following ART initiation.

Study setting

The study was conducted at the adult clinic of AIDS Prevention Initiative in Nigeria (APIN), Jos University Teaching Hospital (JUTH) Jos Plateau state. The clinic currently provides ambulatory HIV care, treatment and support to about 9,000 patients within Jos and the neighboring provinces. The clinic is supported by the US government through the President's Emergency Plan for AIDS Relief (PEPFAR).

Source of data

Data were extracted from three databases; the pharmacy, laboratory, and patient clinic visit. The database was a FileMaker Pro software version 10.5, transferred to an Excel spreadsheet. The data extracted included: (i) demographic data: age and sex; (ii) laboratory data: serum creatinine (SCr), CD4 lymphocyte counts, HIV-1 RNA viremia (viral load – VL); (iii) clinical data: body weight, comorbid conditions (diabetes, hypertension), co-infections with hepatitis B or C viruses, co-administration of nephrotoxic agents such as non-steroidal anti-inflammatory drugs (NSAIDS), cotrimoxazole, acyclovir, streptomycin, angiotensin-converting enzyme inhibitors and amphotericin B.

Baseline and endpoint glomerular filtration rate (GFR) were determined for each available SCr value using the nearest age and body weight. Creatinine clearance was determined using the Cockcroft-Gault formula. CD4 lymphocyte count and VL at baseline and 48 weeks were defined as those values estimated proximal to the date of the baseline and endpoint SCr, respectively.

Operational definition

Renal impairment is defined as GFR <60 mL/min/1.73 sqm (with or without kidney damage), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation[22,23] which according to the Kidney

Disease Outcomes Quality Initiative constitutes moderate (stage 3) kidney disease.[24]

Baseline serum creatinine (SCr) is defined as the first recorded SCr prior to ART initiation. The study endpoint was defined as each patient's first episode of nephrotoxicity or the date at which the last available SCr value before 31st December 2012 was obtained.

Statistical analysis

Baseline characteristics of normally distributed continuous variables were described using means and standard deviations. Median and interquartile range were used for continuous variables that did not show normal distribution. Categorical variables were summarized using proportions or frequencies. Chi-square test of independence was used to determine the significant association between renal impairment and TDF exposure. Bivariate analysis using the Chi-square test was performed to determine the probable risk factors that are independently associated with the development of renal impairment. The risk factors included: sex, age, weight, TDF exposure, baseline CD4 count and HIV RNA viral load, use of nephrotoxic medications (like acyclovir, non-steroidal anti-inflammatory agents, amphotericin B and trimethoprim-sulfamethoxazole), co-infection with hepatitis B virus, co-infection with hepatitis C virus, comorbidities such as hypertension and/or diabetes. Risk factors with a p value less than 0.2[12] were included in the final model analysis. Variables with $p<0.05$ were considered statistically significant. Stata version 12 (College Station, Texas, USA) was used to analyze the integrated study data.

Ethical approval

Ethical clearance was obtained from the Research and Ethics Committee of Jos University Teaching Hospital (JUTH/DCS/ADM/127/XXII/5420) on 15th January 2013, and the Harvard School of Public Health Institutional Review Board, Boston USA on 19th June 2013.

Results

A total of 5494 patients were initiated on treatment during the study period. Ninety-five (95) subjects were excluded from the study on the basis of loss to follow up, 55 records were considered invalid and excluded from the analysis due to missing data (20 had no demographics, 17 without baseline SCR measurement, 18 with no baseline hepatitis B and C seropositivity results). Additionally, 71 subjects who had renal impairment at baseline (GFR <60 mL/min/1.73 sqm) were excluded. Therefore 5273 were included in the final analysis (Figure 1).

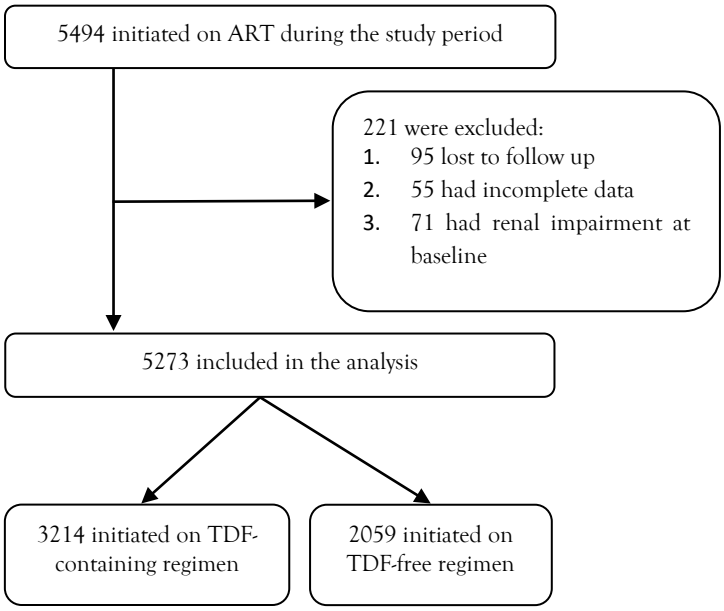


Figure 1. Patient recruitment flowchart

Demographic and baseline characteristics

The study participants were predominantly female (67.1%), had a mean age of 39±9.0 years and a mean weight of 58.67±11.8 kg (Table 1). The median baseline CD4 was 184 cells/cmm (IQR = 106.0, 260.0) while the median baseline log transformed RNA viral load was 4.6 (IQR = 4.0, 5.2). The baseline median creatinine clearance was 75.0 mL/min (IQR = 63.6, 91.0) while the baseline GFR was 107.5 mL/min/1.73 sqm (IQR = 102.5, 113.6).

Table 1. Demographic and baseline characteristics

Variables	Frequency/ Mean/Median	%/SD/(IQR)
Gender		
Male	1737	32.9
Female	3536	67.1
Total	5273	100.0
Age (years), mean	39.13	9.0
Weight (kg), mean	58.67	11.8
CD4 (baseline) (cells/cmm), median	184.0	(106.0, 260.0)
CD4 (48 weeks) (cells/cmm), median	314.0	(180.0, 469.0)
HIV RNA viral load (baseline) (log_{10} copies/mL), median	4.62	(4.0, 5.2)
HIV RNA viral load (48 weeks) (log_{10} copies/mL), median	3.02	(2.3, 4.51)
Creatinine clearance (baseline) (mL/min), median	75.0	(63.6, 91.0)
Creatinine clearance (48 weeks) (mL/min), median	68.5	(53.1, 83.5)
GFR (baseline) (mL/min/1.73 sqm), median	107.5	(102.5, 113.6)
GFR (48 weeks) (mL/min/1.73 sqm), median	103.5	(88.3, 126.1)

GFR – glomerular filtration rate; **IQR** – interquartile range; **SD** – standard deviation.

Characteristics of patients according to TDF exposure status

Table 2 shows that a significantly higher proportion of males compared to females were exposed to TDF (70% versus 56%; p<0.001), while the mean age of TDF-exposed subjects was significantly higher than that of TDF-unexposed subjects (mean age of 40 versus 38 years; p<0.001). Additionally, baseline CD4 cell count was lower in TDF-exposed compared to TDF-unexposed subjects (median (IQR) CD4 cell count of 173.0 (86.0, 1349.0) compared to 196.0 (131.0, 268.0; p<0.001), whereas, baseline viral load was higher in the TDF-exposed patients. Creatinine clearance and GFR of patients in the TDF treated arm were significantly lower than those of the TDF free arm at baseline (83.7 mL/min versus 90.3 mL/min; p<0.001 and 106.9 versus 108.3; p<0.001). Both hepatitis B or C co-infections were more frequent at baseline in patients initiated on TDF (680 versus 140; p<0.001 and 384 versus 148 p<0.001).

Cumulative incidence of renal impairment among TDF exposed/unexposed HIV infected individuals

The cumulative incidence of kidney toxicity among TDF exposed/unexposed HIV infected patients is summarized in Table 3. At 48 weeks, 148 (4.6%) patients in the TDF-exposed arm had renal impairment; that is 46 cases per 1000 persons compared to 47 (2.3%) in the TDF-unexposed arm, representing 23 cases per 1000 persons.

Bivariate analysis of TDF exposure with renal impairment showed a twofold increased likelihood of developing renal impairment relative to the unexposed group (OR=2.0, p<0.001) as presented in Table 3.

Table 3. Incidence of renal impairment among TDF exposed/unexposed HIV infected individuals at 48 weeks of treatment

Renal Impairment	TDF exposure		Odds ratio (95%CI)	Statistics/ p value
	Yes	No		
Yes	148 (4.6%)	3066 (95.4%)	2.0 (1.48-2.89)	Chi-square=19.0 p<0.001
No	47 (2.3%)	2012 (97.7%)		

Bivariate analysis of risk factors associated with renal impairment

Table 4 presents results for the bivariate analysis of risk factors for renal impairment. Variables with p≤0.2 following bivariate analysis included: gender (OR=1.27), older age (OR=1.07), TDF exposure (OR=2.07), baseline GFR (OR=0.98), hepatitis C virus seropositivity (OR=1.62), concurrent use of nephrotoxic

Table 2. Univariate analysis of baseline characteristics of the cohort

Factors	All patients	N (%)/Median (IQR) TDF exposure		Statistic/p value
		Yes (n=3214)	No (n=2059)	
Gender				
Male	1737 (32.9%)	1214 (69.9%)	523 (30.1%)	Chi-square=91.341
Female	3536 (67.1%)	1995 (56.4%)	1541 (43.6%)	p<0.001
Age (years), mean		39.8±9.2	38.02±8.7	T=7.0 p<0.001
≤39 years		1735 (57.2%)	1298 (42.8%)	Chi-square=42.138
>39 years		1479 (66.0%)	761 (34.0%)	p<0.001
Weight				
<57 kg		1458 (63.6%)	834 (36.4%)	Chi-square=12.058
≥57 kg		1756 (58.9%)	1225 (41.1%)	p<0.001
CD4 at baseline (cells/cmm), median		173.0 (86.0, 1349.0)	196.0 (131.0, 268.0)	K.Wallis H=24.2530 p<0.001
≤184 cells/cmm		572 (59.8%)	385 (40.2%)	Chi-square=0.686
>184 cells/cmm		2642 (61.2%)	1674 (38.8%)	p=0.407
HIV RNA viral load at baseline (log_{10} copies/mL), median		4.7 (4.04, 5.2)	4.6 (3.8, 5.1)	K.Wallis H=4.507 p=0.033
<4.62 (log_{10} copies/mL)		417 (52.9%)	371 (47.1%)	Chi-square=25.120 p<0.001
≥4.62 (log_{10} copies/mL)		2797 (62.4%)	1688 (37.6%)	
Creatinine clearance (mL/min), median		83.7 (70.09, 97.7)	90.3 (77.2, 106.5)	K.Wallis H=129.1 p<0.001
GFR (mL/min/1.73 sqm), median		106.9 (102.0, 112.4)	108.3 (103.5, 113.9)	K.Wallis H=39.34 p<0.001
HBsAg				
Positive		680 (82.9%)	140 (17.1%)	Chi-square=197.657
Negative		2614 (56.9%)	1979 (43.1%)	p<0.001
HCV Ab				
Positive		384 (72.2%)	148 (27.8%)	Chi-square=31.775
Negative		2910 (59.6%)	1971 (40.4%)	p<0.001
Comorbidities				
Yes		120 (2.2%)	78 (1.4%)	Chi-square=0.005
No		3174 (58.6%)	2041 (37.7%)	p=0.942

GFR – glomerular filtration rate; **HBsAg** – hepatitis B surface antigen; **HCV Ab** – hepatitis C virus antibodies; **IQR** – interquartile range.

medications (OR=1.46) and comorbid conditions (OR=4.47).

Logistic regression analysis of risk factors associated with renal impairment

Multivariate regression analysis identified older age (OR=1.06, p<0.001), TDF exposure (OR=1.85, p<0.001) and presence of comorbidities (OR=2.71, p<0.001) as positive predictors of renal impairment (Table 5).

Discussion

Cumulative incidence of renal impairment in the study population

We report a higher cumulative incidence of renal impairment among the TDF-exposed compared to TDF-unexposed patients. After one

Table 4. Bivariate analysis of risk factors for renal impairment

Factors	Unadjusted OR (95%CI)	p value
Gender		
Male	1.27 (0.93-1.68)	0.130
Female (Ref)		
Age (years)	1.07 (1.06-1.09)	<0.001
Weight (kg)	1.01 (0.99-1.02)	0.283
TDF exposure		
Yes		
No (Ref)	2.07 (1.48-2.88)	<0.001
Baseline log VL (median)		
<log 4.62		
>log 4.62 (Ref)	1.34 (0.69-2.59)	0.383
Baseline CD4 count (cells/cmm)	0.99 (0.98-1.01)	0.226
Baseline GFR (mL/min/1.73 sqm)	0.98 (0.97-0.99)	0.001
HBsAg		
Positive		
Negative (Ref)	1.13 (0.77-1.66)	0.523
HCV Ab		
Positive		
Negative (Ref)	1.62 (1.08-2.42)	0.020
Nephrotoxic drug exposure		
Yes		
No (Ref)	1.46 (1.06-1.99)	0.018
Comorbid conditions		
Yes		
No (Ref)	4.47 (2.94-6.80)	<0.001

CI – confidence interval; **GFR** – glomerular filtration rate; **HBsAg** – hepatitis B surface antigen; **HCV Ab** – hepatitis C virus antibodies; **OR** – odds ratio; **Ref** – reference.

year of antiretroviral therapy, treatment-naïve patients treated with a TDF containing regimen had a twofold risk of developing renal impairment (GFR <60 mL/min/1.73 sqm) compared to those treated without TDF (OR=2.0, p<0.001). This finding is in agreement with a recently published retrospective cohort study of over 15,000 patients in South Africa which found a small but significant reduction in renal function after 48 weeks on TDF containing therapy.[20] Similarly, another study in Zambia by Mulenga et al. observed that TDF treated patients with mild baseline renal injury were more at risk of progressing to moderate or severe renal impairment than their TDF untreated counterparts in the first year of antiretroviral therapy.[25] Nishijima and his colleagues reported an incidence of renal toxicity in TDF and abacavir group as 9.84% and 4.55% respectively after 48 weeks of antiretroviral therapy.[26] It is also in agreement with the findings of Manfredi and Calza, who reported that a higher proportion of TDF-treated individuals developed renal dysfunction (>50% decline in baseline GFR) at the end of 48-weeks follow-up relative to their TDF-untreated counterparts (7.8% vs 1.3%, respectively; p<0.001).[27] Another large retrospective study conducted by Scherzer and colleagues in 2012 investigated the relationship between TDF use and renal status among 10,841 HIV infected patients, and reported a 33% higher risk of developing chronic kidney injury per annum of TDF exposure (95%CI=18%-51%; p<0.001) after controlling for other independent predictors.[28] This positive association between TDF exposure and the development of renal impairment can be attributed to its mode of excretion. TDF is excreted in the urine by

Table 5. Logistic regression analysis of risk factors for renal impairment

Factors	Adjusted OR (95% CI)	p value
Gender		
Male		
Female (Ref)	0.75 (0.55-1.04)	0.082
Age (years)	1.06 (1.05-1.08)	<0.001
TDF exposure		
Yes		
No (Ref)	1.85 (1.31-2.60)	<0.001
Baseline GFR (mL/min/1.73 sqm)	0.99 (0.98-1.01)	0.077
HCV Ab		
Positive		
Negative (Ref)	1.2 (0.79-1.83)	0.398
Nephrotoxic drug exposure		
Yes		
No (Ref)	1.14 (0.82-1.58)	0.426
Comorbid conditions		
Yes		
No (Ref)	2.71 (1.72-4.25)	<0.001

CI – confidence interval; **HCV Ab** – hepatitis C virus antibodies; **OR** – odds ratio; **Ref** – reference.

glomerular filtration and proximal tubular secretion. The epithelial cells of the proximal tubule have a strong affinity for tenofovir molecule due to the presence of a peculiar set of cell membrane transport proteins that support influx of tenofovir. This prolonged interaction renders the proximal tubule vulnerable to the deleterious effect of the drug.[29]

This finding is in contrast with early randomized clinical trials and post-marketing data which reported TDF to be free of renal toxicity in relatively healthy HIV infected individuals.[30,31] This conflict may be attributed to the fact that clinical trials employ rigid enrollment criteria whereas patients in real clinical settings may have comorbidities, coadministered drugs, or clinical characteristics that may predispose to TDF nephrotoxicity. A Nigerian retrospective cohort analysis of 186 patients by Agbaji et al. found a slight decline of 4.8% in eGFR in the TDF treated arm compared to a gain of 5.1% in the TDF untreated arm, which was not significant at 48 weeks.[32] The difference between the study by Agbaji et al. and this present study may be due to the difference in sample size (186 vs 5273 subjects), as well as the study time period. Similar studies undertaken in South Africa, Zambia, Uganda and Tanzania found no difference in the renal function of TDF exposed patients compared with TDF unexposed cohorts.[20,25,33,34] De Waal et al. in a study of over 15,000 patients followed up for a median duration of 51 weeks reported an improvement on the kidney function of TDF treated patients that had mild renal dysfunction (<90 mL/min/1.73 sqm) at baseline.[20] The reasons for this difference may be attributed to the demographic and baseline clinical characteristics of the study population, as well as follow-up time.

O'Donnell et al. (2011), in a retrospective cohort study of 514 subjects reported that TDF exposed patients on therapy for an average duration of 93 weeks were less likely to develop renal impairment (p=0.01).[10] The contrast between O'Donnell's findings and the present study may be due to a number of reasons. The larger sample size that this present study has gives it more statistical power. In addition, while

O'Donnell et al. recruited predominantly Caucasian subjects (59.7%), all participants of this present study were Africans, who have been found to be genetically predisposed to the development of renal diseases.[35] Also, subjects recruited in this study were immunosuppressed (CD4 <200 cells/cmm) compared to the subjects that O'Donnell et al. enrolled. Furthermore, baseline viral load of participants enrolled for this study was twice higher (4.62 $\log_{10}$ copies/mL) than those enrolled in O'Donnell's study (2.0 $\log_{10}$ copies/mL). Therefore, cohorts in this study were at a higher risk of renal impairment due to severe immune suppression and high viral load.

Other factors independently associated with renal impairment

We found a 6% higher risk of renal toxicity ($p<0.001$) for every 10-year increase in age. Other positive predictors associated with renal function decline were TDF exposure ($p<0.001$) and comorbid conditions ($p<0.001$), while low weight, exposure to nephrotoxic agents, hepatitis B, and C were not associated with renal impairment. This is to some extent in tandem with previous findings. Scherzer et al. observed that co-administration of nephrotoxic drugs, lower body weight, aging, and immunosuppression were positive predictors of impaired kidney function.[28] A recent retrospective cohort study reported older age, comorbid conditions like diabetes, lower CD4 count and underweight as risk factors for renal dysfunction.[12] Older age is known to be a significant predictor of chronic renal dysfunction in the wider society. The average reduction in renal function in the healthy population is estimated at 0.4 mL/min per annum as a result of advancing age.[36] Our study revealed that presence of comorbidities like diabetes and/or hypertension are associated with a 2.7-fold higher likelihood of developing renal dysfunction compared to those without comorbid conditions. Diabetes- and hypertension-associated nephropathies contribute to the progression of chronic kidney disease in HIV infected individuals.[10,16]

Our study had several limitations. First, it was a retrospective cohort study and not a randomized controlled one which might have made it difficult to completely control for confounders. Second, participants with incomplete data for analysis were excluded; the extent to which this affected the findings of this study could not be ascertained. Also, our study defined renal impairment based on a single point measurement of estimated GFR (<60 mL/min/1.73 sqm). However, the endpoint eGFR assessed at 48 weeks was uniform for all patients, which provided adequate information on the renal status of the patients at that time.[13] Furthermore, we may have underestimated the incidence of TDF associated nephropathy. This is because the only marker of TDF-induced renal dysfunction considered in this study was eGFR <60 mL/min/1.73 sqm based on elevation of serum creatinine, which remains normal until over half of the nephrons have been destroyed. Therefore, studies aimed at investigating early kidney tubulopathy using more sensitive biomarkers are hereby recommended.

The introduction of tenofovir alafenamide (TAF) recently approved for clinical use holds a lot of promise in the management of HIV. TAF is reported to be devoid of renal and bone adverse effects.[37] Unlike TDF, which is first metabolized to tenofovir in the plasma and subsequently phosphorylated intracellularly into the pharmacologically active metabolite tenofovir diphosphate (TFV-DP), TAF is thought to be predominantly transformed to TFV-DP intracellularly.[37,38] TAF therefore transports TFV to HIV target cells at a much lower dose than TDF, resulting in lower plasma concentrations of TFV and minimal exposure to the kidneys. Although short term studies report the renal safety of TAF relative to TDF, reports following long term use of TAF are not yet available. However, there is evidence to believe that TAF based regimen is a safer alternative to TDF and will become the mainstay of HIV management in the nearest future.

Conclusion

This study revealed that treatment-naïve Nigerian patients are at a twofold higher risk of developing renal impairment when placed on TDF-containing regimen at 48 weeks compared

with their counterparts that are treated without TDF. In addition, older age and presence of comorbidities are significant predictors of kidney injury. We believe that in no distant time, TAF containing regimen, which is a preferred option to TDF, will be made available to patients living in resource poor settings like Nigeria. Meanwhile, we recommend regular monitoring of renal function of TDF-treated individuals, especially in high risk patients in order to either adjust the dose or withdraw the drug completely at the first sign of nephrotoxicity. With the scale up of the use of TDF-based regimen in Nigeria, there is need to raise awareness about this harmful occurrence.

Authors' contributions statement: BVO designed the study and drafted the manuscript. PU performed statistical analysis and background literature review for the manuscript. BVO, IOA, AP, OOA and SSG provided intellectual support and critically edited the manuscript. All authors read and approved the final version of the manuscript.

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