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A longitudinal study of renal function outcomes in a cohort of HIV patients on tenofovir-based antiretroviral therapy in Ashanti region, Ghana

E. Ahenkan[1,2], P. Kolibea Mante[1], E. Boakye-Gyasi[1]

[1]Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST, Kumasi, Ghana
[2]Kumasi Centre for Collaborative Research in Tropical Medicine, KNUST, Kumasi, Ghana

ABSTRACT:

— ***Objective:*** Tenofovir disoproxil fumarate (TDF), an integral component of first-line antiretroviral therapy (ART), is associated with nephrotoxicity, including a decline in glomerular filtration rate (GFR). The study describes renal function outcomes and risk factors for TDF-associated renal impairment in a Ghanaian cohort who had no known risk factors for renal impairment.

— ***Patients and Methods:*** We included 97 HIV patients who were antiretroviral-naïve at baseline, initiated a TDF-based ART between 2010 and 2018, and had documented baseline renal function tests. We measured follow-up creatinine and urea levels and calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. We described changes in eGFR from ART initiation using paired *t*-test.

— ***Results:*** In patients with eGFR >90 ml/min and <90 ml/min at baseline, the mean eGFR change was -5 ml/min (95% CI: -13-2.7, $p = 0.1981$) and 31 ml/min (95% CI: 23-39, $p < 0.0001$) respectively. All 5 patients in whom TDF was initiated in error (baseline eGFR <50 ml/min), had eGFR above 60 ml/min during follow-up. Overall, 5 (3.9%) patients experienced moderate renal impairment (eGFR; 30-59 ml/min) and no incidence of severe renal impairment (eGFR; <30 ml/min). Patients who had been on treatment for <24 months had a mean eGFR change of 21 ml/min (95% CI: 12-31, $p < 0.0001$) but no significant change was observed in those who had been on treatment for >24 months. Significant associations with decreased eGFR included longer duration of treatment and older age.

— ***Conclusions:*** TDF-associated renal impairment was uncommon; however, the risk increases with age and long-term treatment. In this setting, regular monitoring of renal function should be targeted at higher-risk patients.

— ***Keywords:*** *Tenofovir, GFR, Antiretroviral therapy, Renal function, HIV.*

INTRODUCTION

Guidelines for starting antiretroviral therapy have progressively shifted away from the initial threshold of less than 200 CD4+ (Cluster of Differentiation 4) cells/µl to test and treat irrespective of CD4+ levels[1,2]. Evidence from clinical trials[3] and observational studies[4,5] has shown that early ART initiation results in fewer HIV complications, better immune recovery, and decreased HIV transmission and mortality. Since 2013, the World Health Organization has recommended a triple regimen containing tenofovir as the preferred first-line option to initiate ART in the treatment-naïve HIV patients[1].

Tenofovir disoproxil fumarate (TDF) has shown comparable efficacy to other regimens that contain Zidovudine, or Abacavir[6-9]. TDF has the added advantage of a better

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Corresponding Author: Ebenezer Ahenkan, MD; e-mail: e.ahenkan@kccr.de

safety profile and availability as a once-per-day combination pill leading to better adherence rate[10]. Despite these advantages, several studies[11] have shown a modest but significant decline over time in the glomerular function of HIV-infected patients receiving TDF compared to those on other regimens. There is also a higher prevalence of renal dysfunction among HIV-infected patients compared to the uninfected population. It is estimated that 5-15% of HIV-infected patients present with reduced glomerular function (eGFR < 60 ml/min/1.73 m^2) prior to ART initiation[12]. Antiretroviral monitoring guidelines, therefore, recommend that patients on TDF-based antiretroviral therapy undergo close monitoring of their renal function[13]. However, the low access to laboratory services in a resource-limited setting (like Ghana) makes regular monitoring of renal function impractical, especially in rural and peri-urban areas. This presents a limitation in the use of TDF-based antiretroviral in this setting. Ghana has a high HIV burden and is classified among the 35 countries that account for more than 90% of people becoming newly infected with HIV[2,14,15].

Even though the effect of TDF on the renal function of HIV-infected patients has been widely studied in literature in cohorts with varying clinical characteristics in other settings, there is limited data from Sub-Saharan Africa[16]. Hence, our study aims to describe renal function outcomes and risk factors for TDF-associated renal impairment in a Ghanaian cohort who had no known risk factors for renal impairment.

PATIENTS AND METHODS

Study Sites

We conducted the study in Kumasi South Hospital and Effiduase Government Hospital in the Ashanti region of Ghana. Kumasi South Hospital (KSH) is a regional hospital whose clients are mostly from the Kumasi metropolis and serves as one of the referral centres in the region. The ART clinic has initiated ART in more than 8,000 patients and currently has about 2,500 patients who attend the clinic regularly. The number of patients on a TDF-based regimen was 656. Effiduase Government Hospital (EG) is a district hospital and provides primary healthcare for most of the people in the rural communities of the district. The ART site was established in 2015 and initiated ART in more than 450 patients, 126 of them on a TDF-based regimen. It now has about 360 patients who attend the clinic regularly. The ART clinics in these hospitals adhere to ART standards and also follow protocols published by the National AIDS/STI Control Programme (NACP) of the Ghana Health Service (GHS) (available at: https://www.ccmghana.net/index.php/policies-guidelines?download=199:art-guidelines-revised-2017).

Study Design

The study is a longitudinal study. Baseline clinical data were obtained retrospectively from participants' folders and included sociodemographic information, clinical findings and laboratory investigations conducted directly before antiretroviral therapy initiation. We included HIV patients who were antiretroviral-naive at baseline, initiated treatment with a TDF-based antiretroviral therapy between 2010 and 2018, had continued treatment for at least 6 months, were 18 years or older and had documented renal function tests conducted directly before ART initiation. We excluded patients with known risk factors for kidney disease, such as diabetes and hypertension, and those on medications for other chronic conditions. We also excluded patients who were noncompliant with their treatment for more than a month and those whose treatment regimen changed during the period. The design and the population used are to limit confounding factors as much as possible, to ensure that the renal function outcomes observed can be linked to TDF exposure and to explore other risk factors in the absence of known risk factors for TDF-associated renal impairment.

All patients who met the inclusion and exclusion criteria and willingly consented to be part of the study were recruited. 102 participants in total were recruited between June 2018 and January 2019; however, data from 97 participants only were used in the analysis, due to contamination of the sera from 5 participants. All participants signed an informed consent form.

For each participant, we collected about 2 ml of blood into a serum separator tube, processed, and measured serum creatinine and urea concentrations using an automatic biochemistry analyser (LE scientific, Horizon 850, China). We assessed the efficacy of medication by the presence or absence of opportunistic infections using the GHS adult clinical assessment form for HIV patients (**Supplementary File 1**).

We calculated the estimated glomerular filtration rate (eGFR) using the following two equations:

1) Modification of Diet in Renal Disease (MDRD) equation, $eGFR = 175 \times SCr^{-1.154} \times age^{-0.203} \times 1.212 \times 0.742$ (if female).
2) Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, $eGFR = 141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$. SCr = standardized serum creatinine (mg/dl), $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (females) or -0.411 (males), min = indicates the minimum of SCr/κ or 1, max = indicates the maximum of SCr/κ or 1.

We used these two equations to assess eGFR distribution at baseline and follow-up. However, we used eGFR calculated with the CKD-EPI formula in the analysis since it has been proven[17] to be more accurate compared to the MDRD formula in patients with stable kidney function.

Statistical Analysis

We analyzed renal function outcomes and the associated predictors using GraphPad Prism® v.6.0 (GraphPad Software Inc., San Diego, CA, USA) We expressed the characteristics of the study participants using means or medians depending on the distribution of the data and

described categorical variables using counts and percentages. We compared baseline and follow-up eGFR using paired *t*-test and performed other comparisons using the Mann-Whitney U test for two independent groups and the Kruskal-Wallis' test for groups of more than two followed by Dunn's multiple comparison test as required. We determined associations and risk factors for reduced eGFR using multiple linear regression models and correlations. All reported *p*-values are two-tailed and for each analysis, we considered a *p*-value lower than 0.05 as significant.

RESULTS

Demographic and Clinical Characteristics

We used data from 97 participants in the analysis. Table 1 shows the socio-demographic and clinical characteristics of the participants. The cohort consisted of 77% women. The median age at ART initiation was 38 years (IQR: 32-45). The median baseline weight was 57 kg (IQR: 45-65). More than 60% of the study population had advanced immunosuppression prior to ART initiation (WHO – HIV clinical stage III and IV). The median length of follow-up was 25 months (IQR: 10.0-80.5). About 45.4% of patients initiated ART treatment with eGFR below 90 ml/min. Of the 97 patients screened, 3 (3.1%) presented with opportunistic infections, which included unexplained chronic diarrhoea, skin rash, and pulmonary tuberculosis.

Table 1. Socio-demographic and clinical characteristics of study population.

Parameter		Number of patients (%) N=97
Sex	Male	22 (22.7)
	Female	75 (77.3)
Baseline age, (years)	21 - 30	18 (18.6)
	31 - 40	38 (39.2)
	41- 50	25 (25.8)
	≥ 51	16 (16.5)
Occupation	Administration	6 (6.2)
	Agricultural	13 (13.4)
	Trading	47 (48.5)
	Vocational	21 (21.6)
	Unemployed	10 (10.3)
Baseline weight, (Kg)	≤ 40	6 (6.2)
	41 - 50	26 (26.8)
	51 - 60	27 (27.8)
	61 -70	26 (26.8)
	≥ 71	12 (12.4)
WHO HIV clinical stage	Stage I	12 (12.4)
	Stage II	23 (23.7)
	Stage III	56 (57.7)
	Stage IV	6 (6.2)
Duration of treatment, (months)	6 - 24	48 (49.5)
	25 - 48	16 (16.5)
	Above 48	33 (34.0)

Table 2. Baseline and follow-up eGFR of study population. eGFR was calculated using CKD-EPI and MDRD formulas, stratified by the Chronic Kidney Disease classification system.

Chronic Kidney classification	Number of patients (%) N=97	
eGFR, (ml/min/1.73 m²)	CKD-EPI	
	Baseline	Follow-up
Stage 1 (≥ 90)	53 (54.6%)	71 (73.2%)
Stage 2 (60-89)	30 (30.9%)	22 (22.7%)
Stage 3 (30-59)	14 (14.5%)	4 (4.1%)
	MDRD	
Stage 1 (≥ 90)	51 (52.6%)	68 (70.1%)
Stage 2 (60-89)	33 (34.0%)	25 (25.8%)
Stage 3 (30-59)	13 (13.4%)	4 (4.1%)

Renal Function Outcomes

Table 2 shows the eGFR distribution at baseline and follow-up with the MDRD and CKD-EPI equations. Overall, 4 patients experienced moderate renal dysfunction (defined as eGFR, 30-59 ml/min). No patient had a severe reduction in eGFR to below 30 ml/min during the period of the study. In all, 53 (CKD-EPI) and 51 (MDRD) participants had eGFR ≥ 90 ml/min at baseline, but these numbers increased to 71 and 68, respectively, during follow-up. At baseline, the number of participants who had mild renal impairment (eGFR, 60-89 ml/min) was 30 (CKD-EPI) and 33 (MDRD), but these numbers decreased to 22 and 25, respectively, during follow-up.

Figure 1 shows the renal function outcomes stratified by baseline eGFR, duration of treatment and sex. There was no difference in the mean baseline eGFR between males (96±32) and females (95±30) ($p = 0.8558$). There was also no difference in the median duration of follow-up between males (19.0, IQR: 8.8-77.0) and females (29.0, IQR: 12.0-82.0) ($p = 0.3442$). However, females experienced a significant mean eGFR increase of 12.0 ml/min (95% CI: 4.7-20, $p = 0.0021$) during follow-up, compared to 7.9 ml/min (95% CI: -5.3-21, $p = 0.2275$) in males.

The duration of tenofovir exposure was not statistically different between the two baseline eGFR groups, i.e., ≥90 ml/min and <90 ml/min groups. In patients with normal eGFR at baseline (≥90 ml/min), mean eGFR decreased by -5 ml/min (95% CI: -13-2.7, $p = 0.1981$). However, a significant improvement in renal function was observed in patients with mild to moderate renal impairment at baseline (eGFR <90 ml/min) with a mean eGFR increase of 31 ml/min (95% CI: 23-39, $p < 0.0001$).

Patients who had received treatment for 24 months or less showed significant improvement in their renal function, with a mean eGFR change of 21 ml/min (95% CI: 12-31, $p < 0.0001$). This change decreased over time; that is, 7.8 ml/min in the 25-48 months group and 2.3 ml/min in the group that had been on treatment for more than 48 months. However, the changes observed in these two groups were not statistically significant.

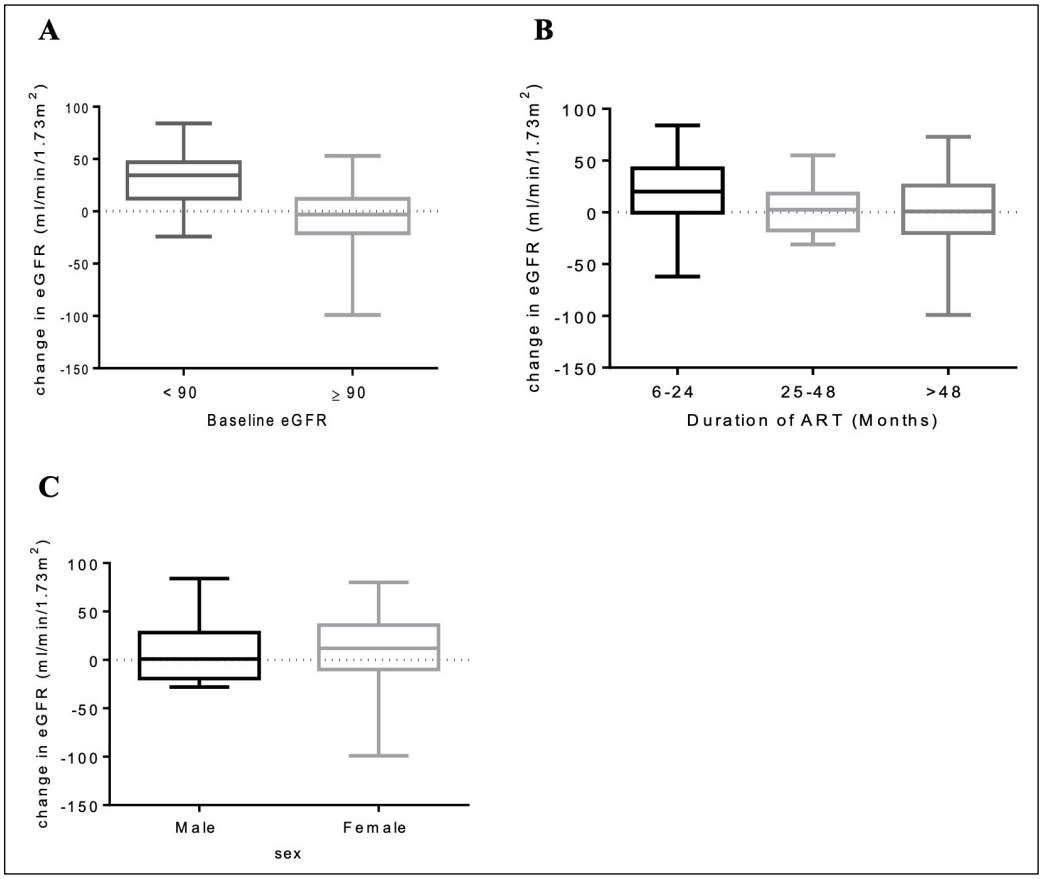

Figure 1. Graphs comparing the change in renal function of patients by baseline eGFR (**A**), duration of treatment (**B**), and sex (**C**). eGFR calculated using chronic kidney disease epidemiology formula. eGFR, estimated glomerular filtration rate; ART, antiretroviral therapy.

Five patients who started treatment with baseline eGFR below 50 ml/min all experienced an improvement (eGFR >60 ml/min) in their renal function after varying durations of the regimen.

Risk Factors

We performed multiple linear regression analysis with eGFR change from baseline as the dependent variable and sex, age, baseline weight, WHO HIV clinical stage, baseline eGFR, and duration of treatment as predictors. Table 3 shows the summary of the results obtained. The combination of variables significantly ($p < 0.0001$) predicted the change in eGFR from baseline. Age ($p = 0.0004$) and baseline eGFR ($p < 0.0001$) significantly contributed to the prediction. From the analysis, we found that for every 1-year increase in age, eGFR decreases by 0.92 ml/min (95% CI: 1.42-0.42). A significant negative correlation (Pearson's $r = -0.241$, $p = 0.0180$) was also found between the change in eGFR from baseline and the duration of treatment.

DISCUSSION

Our study observed that HIV patients on TDF-based ART generally experienced an improvement in their renal function, especially those with mild to moderate renal impairment at ART initiation. Similar results have been reported in several studies[14,18,19] conducted in other African countries. Since the majority (64%) of the participants started treatment at an advanced immunosuppression state (WHO – HIV clinical stages 3 and 4), the

Table 3. Simultaneous multiple regression for factors predicting changes in eGFR in study population.

Variable	ß	95% CI	*p*-value
Sex	1.130	-10.26 - 12.53	0.8442
Age	-0.9198	-1.416 - -0.4232	0.0004
Baseline weight	-0.2586	-0.6797 - 0.1624	0.2255
WHO clinical stage	-2.241	-8.518 - 4.036	0.4800
Baseline eGFR	-0.8207	-0.9920 - -0.6494	<0.0001
Duration of treatment	-0.04110	-0.1843 - 0.1021	0.5700
Constant	146.3	96.62 - 195.9	<0.0001

ß – regression coefficient, CI – confidence interval.

general improvement in renal function may be due in part to effective treatment of underlying HIV-associated nephropathy (HIVAN), as well as resolution of opportunistic infections. HIV infection has been identified as a risk factor for renal impairment[20]. Highly active antiretroviral therapy (HAART), together with standard therapy for chronic kidney disease, is the recommended treatment for HIVAN[21]. A sustained viral suppression, due to ART initiation, can therefore result in significant improvement in renal function and that can offset the small reduction that may be caused by tenofovir. The resolution of opportunistic infections and the subsequent discontinuation of nephrotoxic medicines used to treat them may all contribute to this improvement. In patients who started TDF-based ART with normal renal function (eGFR ≥90 ml/min), a small decline in eGFR was observed, even though not statistically significant. ART may only improve kidney function if there is HIV-associated renal impairment[19]. The small reduction observed in this group may have been caused by TDF and/or other factors, such as ageing. It has been suggested[16,22] that the decline in renal function observed in patients taking TDF-based antiretroviral may be due to the inhibition of tubular creatinine excretion rather than a decrease in glomerular function.

Women experienced a significant improvement in renal function compared to men even though their baseline eGFR and duration of ART treatment were not statistically different. A similar result was reported by Kamkuemah et al[14]. They found that women experience a faster rate of increase in eGFR over time compared to men in patients on TDF-based antiretroviral.

Improvement in renal function may be more prominent at the initial phase of ART as patients who had been on ART for 6-24 months experienced a significant improvement in renal function compared to the other groups who had been on treatment for more than 24 months. For patients who had been on treatment for more than 24 months, mean eGFR generally remained near baseline levels. This is consistent with some studies[20,23] which reported that there seems to be stabilization in renal function after a longer period on TDF.

Five patients who initiated tenofovir with eGFR below 50 ml/min were not eligible for TDF-based ART, according to the antiretroviral therapy guidelines in Ghana[24] and other international guidelines[2]. TDF-based ART was initiated in error in these patients, due to the routine use of absolute creatinine levels instead of calculated eGFR for convenience. The improvement in renal function observed in this group of patients provides some form of reassurance in a resource-limited setting like Ghana, where some patients initiate TDF without baseline renal function assessment. Bedimo et al[25], in their systematic review, stated that no significant worsening of eGFR was reported in such patients, and in one of the reported studies (STaR), improvement in eGFR was detected.

The current study observed that patients who initiated treatment with lower eGFR (< 90 ml/min) were likely to experience a positive change in renal function compared to those who began with eGFR above 90 ml/min. Older patients were at increased risk of decline in eGFR compared to younger patients. TDF-based ART, in the long term, appears to cause a decline in renal function; however, the decline seems to occur at a slower rate. Older age and long-term exposure to TDF have also been identified as risk factors for TDF-associated renal impairment in another study[26] conducted in a Ghanaian population.

Limitations

The study has some limitations. We had no data on concomitant medications that were taken by participants to treat acute conditions. Some of these medicines may influence some of the renal function outcomes that we observed. That notwithstanding, patients on long-term medications for other conditions were excluded. Actual tenofovir exposure may not correlate with the duration of treatment in some participants due to non-compliance. To minimize this, we excluded patients who were noncompliant with their treatment for more than a month.

CONCLUSIONS

TDF-associated renal impairment was uncommon; however, the risk increased with age and long-term treatment. In this setting, the absence of routine renal function testing facilities should not preclude the use of TDF in patients without any known risk factors for renal impairment. That notwithstanding, renal function should be regularly monitored in the elderly, in patients with long exposure to TDF and in those at higher risk.

Ethics Approval:
The Committee on Human Research, Publication, and Ethics, KNUST, School of Medical Sciences, and Komfo Anokye Teaching Hospital reviewed the research protocol and gave ethical approval for the study (approval number: CHRPE/AP/317/18).

Informed Consent:
Written informed consent was obtained from all subjects enrolled.

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Authors' Contribution:
EA was involved in study design, data collection, and data analysis, and wrote the manuscript. PKM and EBG were involved in the study design, and data analysis and edited the manuscript. All the authors read and approved the final manuscript.

ORCID ID:
Ebenezer Ahenkan: 0000-0002-7410-9995
Priscilla Kolibea Mante: 0000-0002-6886-7570
Eric Boakye-Gyasi: 0000-0002-5723-7266

Conflict of Interest:
The authors declare that they have no conflict of interest to declare.

Availability of Data and Materials:
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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