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Research

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Incidence and association of renal dysfunction with a long term Tenofovir-based therapy among HIV-positive naïve cohort at Ronald Ross Hospital

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Abstract

Introduction: *Tenofovir-based antiretroviral therapy places HIV-infected patients at high risk of renal dysfunction. Therefore, we evaluated if the incidence of renal dysfunction in adults HIV positive patients with long term tenofovir-based regimen use is higher than in those without Tenofovir use.* ***Methods:*** *we performed a retrospective cohort analysis of 834 HIV positive patients at the counselling and testing center at Ronald Ross General Hospital. Patients´ records in data management software called SMARTCARE from 2008 to 2012 were reviewed to compare renal function between patients on tenofovir-containing regimen (447) with non-Tenofovir containing regimen (387). We evaluated glomerular filtration rate using creatinine clearance, serum creatinine, urea and exposure to TB medication, Cotrimoxazole use and CD4 cell count. Multivariable logistic regression was used to determine the factors associated with renal dysfunction. We report multivariable hazard ratios, risk ratios and linear outcomes with predictors retained if P < 0.05. Potential predictor variables included in the multivariable models were age, sex, weight, serum creatinine and treatment with tenofovir.* ***Results:*** *the CD4 cell count, urea, anti-TB medication, Co-trimoxazole use, education level, employment status and creatinine clearance were similar at baseline between the two groups. Tenofovir-exposed patients had a relative increase in serum creatinine (P<0.04) and decline in creatinine clearance at 18 months during treatment (P<0.16)) relative to non-tenofovir exposed patients; Tenofovir exposed patients had a risk of developing renal dysfunction more than the non-tenofovir-exposed group (OR: 4.5, 95% CI, -1.71-10.7, P<0.032). Further, serum creatinine µmol/L increase (OR: 0.1, 95% CI, -0.43-(-0.40, p<0.02)), age per year-increase (OR: 0.75, 95% CI -1.28-(-0.34), P<0.01), body weight per 1 kg-increase (OR: 0.65, 95% CI, 0.015-1.07, P<0.04) and gender are risk factors to renal dysfunction.* ***Conclusion:*** *tenofovir-based therapy is associated with decline in renal function, with most developing mild renal dysfunction. The need for close renal monitoring of patients initiated on tenofovir by using creatinine clearance is recommended and use of less renal toxic Tenofovir-Alafenamide (TAF) analogue.*

Introduction

Many of the countries in Africa have developed and expanded their response to the Acquired Immunodeficiency Syndrome (AIDS) epidemic, and increased access to antiretroviral treatment [1,2]. This includes the provision of antiretroviral drugs to patients eligible to start, improved patient management and care, and expanded programmes to reduce transmission. In Zambia, southern Africa, the choice is use of a nucleotide Reverse Transcriptase Inhibitor (NRTIs), Tenofovir Disoproxil Fumerate (TDF) and Emtricitabine (FTC) and Non-Nucleoside Reverse Transcriptase inhibitor efavirenz (EFV) or nevirapine (NVP) as first line treatment regimen [3]. Tenofovir disoproxil fumerate is an oral pro-drug of tenofovir, a nucleotide reverse transcriptase inhibitor (NRTIs) that has been indicated for use in antiretroviral therapy (ART) patients [3]. It´s currently a recommended first-line agent in combination with other antiretroviral for HIV management in Zambia, because of its favorable pharmacokinetic profile, good antiviral potency and high tolerability [3-5]. Zambia adopted the use of TDF in first line regimen for management of HIV in 2007 [3,6]. This means all newly eligible HIV patients for antiretroviral drugs start with this drug combination containing TDF as in Table 1. TDF has been considered safe and associated with fewer side-effects in many clinical trials [7-9]. However, there have been many case reports and cohort studies such as this one describing TDF-associated nephrotoxicity [1,10-12].Tenofovir has been associated with renal abnormalities [13] and several studies have shown that tenofovir can cause mild to moderate renal dysfunction [11-15].

In many studies recommendations and guidelines have been made that monitoring of renal function should be done by use of creatinine clearance

rather than measurement of serum creatinine and urea only. In this study interest was to determine incidence of renal dysfunction on patients on ART exposed to TDF and those not, thereafter evaluating the significance of performing creatinine clearance in intervals in such patients. Although highly active Antiretroviral Therapy (HAART) has had little influence on the incidence of end stage renal disease, Pichit *et al.* correlated the introduction of HAART with a declining incidence of Chronic Kidney Disease (CKD) in a cohort of 4,509 individuals with HIV [13]. Since such patients are on these drugs for a long period of time, Lloyd *et al.* recommend that if Tenofovir is used as first line regimen, as is the case in Zambia, benefits should be weighed against the more intensive renal monitoring [10]. Further recommends that because of the extensive prescription of tenofovir for ART patients´ warrants longer-term studies with greater consideration of confounding variables, such as comorbidities and the other medications used. In this study, we describe changes in renal function in ART patients on tenofovir containing and a non-tenofovir containing regimen with follow up through 18 months. We also followed and considered other important potential confounders such as patient demographics, baseline laboratory investigations, and other medications prescribed.

Methods

We performed a retrospective cohort analysis of 1,342 HIV infected patients at Ronald Ross General Hospital in Mufulira district Zambia. All HIV positive patients aged 15 to 45 years old who were enrolled at the Counselling and Testing Center (CTC) at Ronald Ross General Hospital on ART regimen from February 11, 2009 through September 15, 2014 were selected. Two treatment groups were considered as depicted from Table 1 and Table 2; Tenofovir containing and a non-tenofovir containing line group. Data were extracted from the SMARTCARE software, patient files and medical notes by a team comprised of biomedical scientist, pharmacist, health information officer, medical doctor and a nursing sister. Data were then entered into excel database then exported into STATA (version 12) for analysis. Study participant recruitment was from 2008 to 2009. All HIV+ patients on ART with normal baseline parameter such as serum Creatinine levels, CD+ cell count, Urea were included in the study with follow up until 2014.The parameters were measured and calculated at 6, 12 and 18 month of follow up for both TDF exposed group and the non-exposed. We defined an ART regimen according to the Ministry of Health Consolidated Antiretroviral Therapy treatment Standard Operating Procedure For adults and adolescents (Ministry Of Health, 2013). We compared the effect of tenofovir with no tenofovir use in these patients on kidney function (defined as changes in Glomerular Filtration Rate (GFR) and serum creatinine (SCr)), CD4 cell count changes, urea levels and changes in weight were also followed).

Study population and data extraction: counselling and testing center at Ronald Ross General Hospital serves various members of the community in Mufulira District. The center has over a population of 7,230 patients on ART. Patients receive multidisciplinary team health care, including counselling, adherence meetings, follow ups and reviews. Data is entered in data management software called SMARTCARE, were demographic, laboratory and other important information are stored. We queried HIV database, and patient registers to identify eligible patients. We captured patient demographics, laboratory results, and medication dispensed using electronic database. All files of patients aged 15 to 45 years old were eligible in this study, and on HAART regimen (NRTIs and NNRTIs) with or without PI. All patients that had no confirmed conditions which increase blood creatinine levels (impaired renal function, chronic nephritis, urinary tract obstruction, HIV-associated nephropathy, muscle diseases such as gigantism, congestive heart disease, shock and others) were included in the study. Patients were excluded if they had no follow up laboratory results (no creatinine clearance before initiation and during therapy or pharmacy data). Additional exclusion criteria included patients who were on any other

antiretroviral drug other than first and second line regimen.

Measurements: we followed appropriate demographic variables (weight, sex, age, employment status, and education level), a complete history of ART, Cotrimoxazole use and anti-Tb medication use from databases and files. The following baseline values (≤60 days of regimen before initiation): age, sex, CD4 cell count (count/uL), serum creatinine (µmol/L), urea (µmol/L), and weight (kg) were obtained. Serum creatinine results were extracted from patient files (423/447, (95%) for tenofovir containing group and (358/387, (93%)) for non tenofovir containing regimen. Creatinine clearance was calculated using the Cockcroft Gault formula using weight taken on the same day that creatinine measurements were done. The Cockcroft-Gault formula has been preferred because it is relatively easy to use compared to the Modification of Diet in Renal Disease (MDRD), which has not been validated in acute renal failure. Since the formula does not adjust for body mass relative to the Cockcroft-Gault formula it underestimates GFR for heavy people and overestimates it for underweight people [2,8,15]. Creatinine clearance was calculated at four (4) time points: before initiation of ART, Six (6) months after initiation of treatment called it first review, at twelve (12) months (second review) and at eighteen (18) months called it third review as depicted in study flow chart. Renal dysfunction at each time point was also classified into stages according to the K/DOQI criterion. Renal dysfunction was categorized according to the K/DOQI criterion with CrCl: CrCl ≥ 90ml/min considered no renal dysfunction; CrCl of 60 - 89ml/min was mild renal dysfunction (K/DOQI stage 2); CrCl of 30 - 59ml/min as moderate dysfunction (K/DOQI stage 3); and CrCl lower than 30ml/min was severe dysfunction (K/DOQI stage 4 and 5). Serum creatinine was categorized as low or high Baseline renal function was further categorized into CrCl < 50 ml/min and <50ml/min. Creatinine clearance that had been calculated already was extracted from the clinical records on patient files, re-calculated and filed.

Statistical analysis and ethical approval: using a prevalence of renal dysfunction at 15% among the HIV infected patients on Tenofovir and 7% among non HIV infected patients [16], sample size of 860 was calculated with 90% likelihood that the percentage of developing drug-related toxicity was different. A minimum sample of 344 HIV patients on ART was considered in each group. Adjusting for loss of follow up and missing values at 80%, 430 were considered as sample size for each group. All continuous variables were assessed for skew and as all (other than urea) had a non-Gaussian distribution. These variables were compared using Wilcoxon rank-sum test and reported by median and interquartile ranges. For categorical variables, frequencies, proportions and percentages were used to describe the participants and chi-square test was used to assess associations between variables. Univariate followed by multivariate logistic regression analyses were performed using Pearson´s correlation coefficient to determine predictors of GFR <50 ml/min/1.73m^2. Adjusted odds ratios were calculated by multivariable logistic regression in order to determine factors independently that are associated with renal dysfunction among HIV patients´ on tenofovir regimen and those not on tenofovir. All reported values are exact and two-tailed, p value of <0.005 was considered significant. Our primary predictor of interest was presence or absence of tenofovir 300mg in the ART regimen analyzed. We measured changes in serum creatinine, GFR, CD4 cell count, urea and weight. We analyzed continuous outcomes of changes in GFR, serum creatinine, and CD4 cell count through repeated measures linear mixed models. We used Cox proportional hazard modelling for dichotomous outcomes of GFR < 50 ml/min or < 50 ml/min. Median changes in CrCl from baseline for those initiated on TDF and non-TDF regimen was calculated at 12 and 18 months. Potential predictor variables included demographics (age and sex); treatment with tenofovir, baseline creatinine, urea, weight and CD4 cell count, history of anti-TB medications use, Cotrimoxazole use, and ART regimen class. We used backward selection and excluded predictor

variables with highest p values singly until the final model contained only predictor variables with p < 0.05. We obtained approval from The University of Zambia Biomedical Research Ethics committee (REF.No.003-07-15). All statistical analysis was performed with the STATA for windows software (Version 12.0).

Results

Baseline characteristics: a total of 1,342 adults and adolescents on antiretroviral drugs were enrolled in this study from February 11, 2008 through to September 15, 2014. After exclusion of some participants due to renal abnormalities, absence of creatinine results before initiation, 834 patients meet the inclusion criteria. Of the 834, 447 (53.6%) were on a regimen containing TDF and 387 (46.4%) were on a non-TDF containing regimen. A total of 153/447 participants on TDF and 123/387 on non-TDF actually completed the follow up of 18 months. This was as a result of non-availability of results. However, this was considered in the design stage and analysis as stated in the methods. At baseline, the TDF exposed group patients were older 36 years (IQR: 30, 42) than the non TDF group 35 years old (IQR: 29, 45), though not clinically significant (p-value=0.21). There were more females than males in this study (Table 3). Most of the participants were females aged 15-34 years old, unemployed and had a secondary level education. Renal function defined by creatinine clearance at baseline before ART initiation was similar in both groups (Figure 1, Figure 2). There were 14 failure events observed during a total of 1399.4 person-years. The longest follow-up time for an individual was 12.7 years.

Incidence and renal dysfunction associated factors: the incidence rate (attack rate) in those exposed to TDF was 15.3 per 1000 per person-year (8.5-27.7) compared to those not exposed to TDF 4.4 per 1000 per person-year (1.4-13.6), 627 records included in analysis. The point prevalence of mild and severe renal dysfunction among HIV-positive adults on TDF-based therapy was 18.4% and 0.2% respectively at 18 months. Relative risk of TDF exposure and non TDF was 3.7 per 100 and 1.5 per 100 respectively. The risk ratio was 2.5 between the exposed and unexposed. The odds ratio between those exposed to TDF and those not exposed was 2.9. In addition, 59.3% of renal dysfunction in this study was attributed to TDF exposure of these participants. The median CD4 cell count for TDF-exposed group and non-TDF expose respectively before initiation of therapy was 211 cells/uL and 240 cells/uL. There was statistically significant difference in CD4 cell count (at 3 time points) between groups, in creatinine (at 18 months), creatinine clearance (at 6 months) and co-trimoxazole use between the two groups (Table 4). Maximum likelihood estimate of the rate ratio (RR) between those exposed to TDF and those not was 0.29. 95% CI 0.08-1.02, p-value=0.04 and log-rank test for equality of survivor function had p-value=0.04.Creatinine clearance calculation was performed in 423 participants (423/447, 95%) on TDF and 358 (358/387, 93%) for non-TDF group at baseline. At 18 months during treatment creatinine clearance was performed on 294/447 (65.8%) patients on TDF and 264/387, (68.2%) on non-TDF regimen. This actually agreed with the highly criticized assumption that HIV patient´s renal functions are primarily monitored by creatinine changes, which is against World Health Organization (WHO) recommendations and Zambia Ministry of Health guidelines. There was no significant difference in baseline weight, renal dysfunction stage and whether the patient was once on TB medication or not between groups. In both unadjusted and adjusted analysis for mean changes in GFR from baseline to 18 months, TDF exposed patients were 2.5 times more likely to have decline in GFR through 6 and 12 months compared with the non-TDF containing group though it was not statistically significant (Table 5). The decline in GFR was more pronounced among TDF-exposed group if the baseline creatinine clearance levels was greater than 80mL/min/1.73m^2, but also if GFR was between 50 and 79mL/min/1.73m^2. The only statistically significant predictors of greater than 50% decline in

GFR or as a continuous outcome measure were baseline age and CD4 cell count at 18 months follow up (Table 6).The sensitivity analysis performed reviewed an Receiver Operating Characteristic Curve (ROC) value of 0.76 which was close to 1 than 0.5 suggesting that classification was not due to chance.

Blood creatinine and creatinine clearance: increase in creatinine was a statistically significant predictor of renal dysfunction unadjusted for other variables (OR: 1.00, 0.98-1.02, P-value=0.056). Exposure to TDF after 18 months of follow up had no statistically significant effect (AOR: 2.28 95% CI 0.98-7.36, P-value=0.529) on renal function in both univariate and multivariate logistic analysis (Table 5). Using the p value <0.05 and 95% CI to define statistically significant potential predictors of renal dysfunction, we found baseline creatinine, age and CD4 cell count at 18 months therapy to be significant predictors of renal dysfunction. In univariate analysis age per year increase <49, baseline creatinine and higher CD4 cell count >500cells/uL were factors less likely associated with renal dysfunction. When we compared the baseline and 18 months creatinine level changes between those on TDF and those on non TDF regimen, we found it was insignificant (p-value=0.86 and p-value=0.08 respectively). Similarly, we compared the baseline and 18 months creatinine clearance changes between those on TDF and those on non TDF regimen. There were both not significantly different (Figure 1, Figure 2). In the adjusted logistic regression (Table 5), all other crude odd ratios were not statistically significant except age and CD4 cell count. Patients aged <49 years than ≥59 (OR: 1.78 (1.03-1.92), p=0.001) were less likely associated with renal dysfunction controlling for baseline creatinine, exposure to TDF, gender, age, baseline CD4+ cell count, weight and urea. In addition, patients with a high CD4+ cell count >500 cells/uL (AOR: 1.24 (0.97-1.07), P=0.051) were less likely associated with renal dysfunction adjusting for weight, age, gender, urea, baseline creatinine and TDF exposure. Baseline urea, medications (TB medication, Cotrimoxazole), baseline weight, age, whether employed or not and education level had no significant effect on renal function in this study. Among the TDF exposed group statistically significant predictors of creatinine rise were increase in age, increased weight and lower CD4 cell count. Among patients with baseline CD4 counts less than 50 cells/uL (74), there was a statistically greater risk of developing increased creatinine with TDF exposed compared with non-TDF exposed patients (AHR: 8.1, 95% CI 1.72, 67.4, p-value=0.03). Comparing the two groups, we observed a steady percentage rise in creatinine and decrease in creatinine clearance on those exposed to TDF compared to the non TDF exposed patients. Although this was not statistically different between the groups (Figure 1 and Figure 2).

Discussion

Renal dysfunction deaths in Zambia stood at 16.37 per 100,000 [17]. Despite been one of the countries affected with high HIV burden there is limited data on renal disease and the risk factors predisposing the population to it. Our primary goal in this study was to evaluate whether Tenofovir Disoproxil Fumerate (TDF) treatment of HIV positive patients alter creatinine clearance (CrCl) and to compared the incidence of renal dysfunction among those exposed to TDF and those not. We found that TDF exposure places HIV positive patients at relative risk of 15.3 per 1000 per person-year to 4.4 per 1000 per person-year to develop renal dysfunction after 12.7 months follow up relative to those not exposed to it. This is an indication of the disease distribution in the population affecting the therapeutic measures currently available. The high incidences can further be explained by the long duration of the disease because renal dysfunction is been missed at follow ups. The high number of missing creatinine clearance calculations attest to this error. The attributable risk due to TDF exposure (59.3%) represents the expected reduction in disease in the population if the exposure could be removed. Considering that these patients are on these drugs for such a long duration, screening at every follow up visit could be intensified. This was further supported with evidence that those

patients exposed to TDF were 2.7 more likely to develop renal dysfunction with 2.9 odds than those not exposed to it. This was quite very interesting because the baseline renal function as estimated by the creatinine clearance was not different between groups at baseline even at 18 months during follow up.

Other studies have found renal dysfunction among those exposed to TDF and had a baseline CD4 cell count <200cells/uL [10,18,19]. In this present study, the median CD4 cell count was 243.9cells/uL for both groups eliminating the assumption that it could have led to renal dysfunction. However, on univariate and multivariate analysis, 3.02 odds and 2.45 existed among those who had a CD4 count between 350 to 500 indicating that their more likely to develop renal dysfunction. This suggests that CD4 cell count could be attributed to and was an important factor predisposing patients to renal dysfunction in this study (Table 6). This is vital because low CD4 cell count has been shown to lower GFR of patients, especially in advanced HIV disease (WHO stage 2 and 4). The only explanation which could explain the variation in incidence rate could be the prevalence, TDF exposure and maybe the duration of the disease in the population. Differences in diet and environment conditions may also have contributed to the results. Despite this our results clearly evidence that our analysis are not due to chance. We found no association between treatment with TDF-based regimen and development of abnormal creatinine clearance at 18 months during treating (P>0.05) on both univariate and multivariate analysis. Indeed the risk exists when exposed to TDF but the effect size (strength of association) was not statistically significant. It however does indicate that renal dysfunction was more likely to occur in the exposed group. Further, the prevalence of mild renal dysfunction in this study was found to be 28.5% which agrees with similar studies done ranging from 27.5% to 42% [10,11,18,20]. The similarity of the baseline creatinine and creatinine clearance in both our patient population as depicted in Figure 1and Figure 2points out an important factor usually ignored by clinicians. On close observation, their existed a steady decline in creatinine clearance at all times points during treatment on those exposed to TDF though the creatinine seemed indifferent between the group. Most of the clinicians in heath institutions would monitor renal function primarily based on blood creatinine and urea levels. However, as it has been shown, quite a number of ineligible patients who should not begin on TDF are been missed at the initiation period, What come out quite surprising also was the insignificant variables such as; gender, baseline creatinine clearance and exposure to TDF in both univariate and multivariate analysis. These variables have been shown by other studies to affect this outcome [9-11,21,22]. We decided not to retain them in the nested model because there were insignificant. Age and weight were confounders and effect modifier and as such the reported rate ratio (RR) was the Mental Hanzal RR and the age-specific rate ratios.

The definition of renal dysfunction also differed in our analysis with other studies such as Freeman *et al.* and Szczech *et al.* who used creatinine as a continuous predictor variable while we used categorical definitions of estimated creatinine clearance. Furthermore and probably many some of these studies that demonstrated a mild or severe renal dysfunction due to TDF had more covariant (diabetes, hepatitis c co-infection) than we did. It can be said that TDF does indeed affect the GRF by decreasing it. However this decrease was not statistically significant between those who were exposed to TDF and those who were not. Prevalence of mild renal insufficiency ranges from 24% in Zambia to 41.2% in Malawi, moderate insufficiency ranges from 7.6% in Zambia to 21.8% in Malawi, and severe insufficiency was under 2% in all studies [10,23-25]. We find a closely similar prevalence. The design of our study, long follow up and the choice of covariates which were used due to recommendations from other similar studies done gives our results significance to our patient population, emphasis on already existing knowledge highlighting the gaps exist in the management of such patients. Other studies could have the ability to control for a variety of many

confounders potentially associated with renal dysfunction. We defined renal dysfunction according to the Kidney Disease Outcome Quality Initiative Classification by GFR (K/DOQI) and further categorized it as CrCl<50 ml/min and CrCl>50ml/min. Our results agree with the other studies done in Zambia that TDF leads to renal dysfunction at 6 and 12 months of follow up [10,11,26]. We have found that at 18 months during TDF and non TDF therapy, there was no clinical difference in creatinine and creatinine clearance between groups (Figure 1, Figure 2).Even though 2 patients exposed to TDF developed renal dysfunction it was partly due to the low baseline CD4 cell count (84 and 80 respectively) at Initiation.

Similarly, the median weight for TDF-exposed was 55.2 kg and 55 kg for non TDF before initiation of ART indicated that less weight may not be an important factor to renal dysfunction in this study. Increases or decrease in weight of patients can affect the creatinine and hence affecting the output in renal clearance. Although it may appear that the decrease in GFR or rise in creatinine is small on the absolute scale, exposure to such therapy for a long period of time is worrisome if no renal monitoring is done. Given the current commitment to long-term ART, small incremental decline in kidney function could eventually lead to kidney failure. Other studies did not found an association of TDF exposure and decline in GFR and some attributed renal effects to other causes. In our study, high risk patients appeared to have increased age and lower CD4 cell count at baseline. It is not surprising that such small incremental decline in renal function could be noticed especially considering that most clinicians do not follow GFR but, rather creatinine. In addition, the gradual increase in CD4 cell count is reassuring because lower CD4 cell count is associated with accelerated kidney function. In this cohort, creatinine clearance monitoring was not consistent and the accuracy of calculation if available was poor. Implementation of TDF in health facilities in which lesser-trained health cadres will be responsible for routine care provisions thus need to be accompanied with assessment tools and protocols to ensure that calculations performed electronically. The strength of our study lies in the fact that we used data from a routine ART programme setting in an established programme using SMART CARE and verified with patients files, which provides a useful complaint to data derived from more controlled and better resource research settings. However, like all clinical cohort studies, not all patients received tests at every point, loss to follow up and thus had missing data. This was considered at design stage, when collecting data and in the analysis. At design we had a similar population between the exposed and unexposed. To minimize loss to follow up, we collected the immediate next values/results done on patients if missing at exact day/month. We also had a limited number of covariates for analysis. All patients had enough measured criteria to be eligible for analysis.

Conclusion

Our study leads further evidence to previous reports from Africa that TDF-associated renal toxicity is rare and if it does occur usually transient. We found no evidence to suggest that TDF had significant impact on renal function in our patient population at 18 months during therapy. Although efficacious, isolated incidences occurred and the long term adverse effects on renal function may limit the use of TDF for patients at higher risk of renal dysfunction. If need be adopt a less renal toxic Tenofovir-Alafenamide (TAF) long-term monitoring of renal function by creatinine clearance in intervals is vital and not just measurement of blood creatinine and urea. The prevalence of mild and severe renal dysfunction among HIV-positive adults on Tenofovir-based therapy was 18.4% and 0.2% respectively at 18 months during therapy. Those patients on TDF who were older than 50 years and presented with CrCl <50 ml/min and a CD4 cell count below 500 cells/uL at baseline were more at risk of developing renal dysfunction.

What is known about this topic

- *There exist an association between Tenofovir-based Antiretroviral therapy and*

renal dysfunction with variations in outcomes reports from different researchers;

- *The renal dysfunction is mild usually reversible if tenofovir is withdrawn;*
- *The independent variable CD4+ cell count as one of the serious outcome determining factor.*

What this study adds

- *Recommendation for a less renal toxic antiretroviral drug Tenofovir-Alafenamide (TAF) analogue;*
- *Re-emphasis on monitoring of renal function with creatinine clearance NOT just serum creatinine/urea. The follow up of such patients for 18 months depicting the prevalence and factors commonly need to pay attention to i.e. CD4+ cell count level variations, age;*
- *The inclusion of independent variables such as co-trimoxazole, urea and TB medication which was absent in most of them.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Enock Wantakisha; original author. Derick Munkonbw; data analysis, review, data analysis and edit of manuscript. Tshula Tumba; scientific review of the results and discussion, design, methodology. Charles Michel; design, review of proposal, methodology, results and recommendation. All the authors have read and agreed to the final manuscript.

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Tables and figures

Table 1: Zambia ministry of health standard ART line regimen (2018)

Table 2: different drug combination categorized into two groups

Table 3: baseline demographic characteristics by class of ART drug combination

Table 4: clinical characteristics of study population

Table 5: univariate and multivariate analysis of renal function as a binary outcome

Table 6: CD4+cell count difference of renal dysfunction in HIV patients on TDF at 18 months follow up by age categories at Ronald Ross Hospital Zambia

Figure 1: blood creatinine at baseline and month 18

Figure 2: creatinine clearance at baseline and month 18

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Table 1: Zambia ministry of health Standard ART line regimen (2018)				
First Line Regimen		**Second Line Regimen**		
	EFV		3TC	
TDF/FTC	Or	AZT	TDF/FTC	LPV/r
	NVP		D4T/3TC	

Table 2: different drug combination categorized into two groups	
GROUP 1 (Tenofovir containing)	**GROUP 2 (Non-Tenofovir containing)**
TDF/FTC/NVP	AZT/3TC/LPV/r,
TDF/FTC/EFV,	AZT/D4T/3TC/LPV/r,
AZT/TDF/FTC/LPV/r	ABC/3TC/EFV
TDF/FTC/LPV/r	ABC/3TC/EFV/NVP
	AZT/3TC/NVP or EFV,
	D4T/3TC/NVP or EFV.

Table 3: baseline demographic characteristics by class of ART drug combination			
Characteristic		**Tenofovir (n=447)**	**Non-Tenofovir (n=387)**
Variable	**Categorized**	n (%)	n (%)
Gender	Male Female	136 (50.56) 310 (55.06)	133 (49.44) 253 (44.94)
Age (years)	15-34	219 (52.64)	197 (47.36)
	35-49	182 (56.70)	139 (43.30)
	50-80	46 (47.42)	51 (52.58)
Education	Primary	130 (48.51)	138 (51.49)
	Secondary	179 (54.74)	148 (45.26)
	Tertiary	67 (58.77)	47 (41.23)
Employment Status			
	Employed	137 (54.37)	115 (45.63)
	Not employed	209 (53.18)	184 (46.82)

Table 4: clinical characteristics of study population			
Variable	**Tenofovir (n=447)**	**Non-Tenofovir (n=387)**	**P value**
CD4 cell count (Count. /uL)			
Before ART initiation†	211 (109, 338)	240 (125, 340)	0.13
6 months†	334.5 (227, 465)	395 (280, 525)	<0.001
12 months†	375 (262, 516)	398 (309, 555.5)	<0.007
18 months†	388 (272, 540)	458 (360, 639)	<0.001
Creatinine (µmol/L)			
Before ART initiation*	64 (22.6)	64 (23.7)	0.86
6 months*	65 (21.5)	63 (21.5)	0.23
12 month	66 (23.2)	63 (25.2)	0.08
18 months*	67 (20.8)	63 (18.7)	0.04
Creatinine Clearance (mL/min)			
Before ART initiation*	106.2 (38.7)	105.8 (35.1)	0.86
6 months†	104.2 (37.2)	111(40.8)	0.08
12 months†	105.4 (38.8)	114 (41.3)	0.01
18 months*	104.9 (35.4)	109.7 (39.5)	0.16
Urea (Mmol/L)			
Before ART initiation†	3 (2.2,3.5)	2.7 (2.1,3.5)	0.07
6 months †	2.6 (2.1, 3.6)	2.9 (2.2, 3.8)	0.22
12 months†	2.9 (2.4, 3.7)	3.2 (2.5, 4.1)	0.01
18 months†	2.8 (2.3,3.5)	3.1 (2.5,3.7)	0.07
Weight (kg)			
Before ART initiation †	55 (49,60.5)	56 (49,62.5)	0.23
6 months†	55.8 (50,62)	55.5 (49,63)	0.66
12 months†	57 (51,62)	57 (49.3,65)	0.57
18 months†	57 (52, 62.5)	55 (51, 63)	0.36
Medication use			
Anti-Tb medication, n (%)			
YES	156 (56.7)	119 (43.3)	0.27
NO	257 (52.6)	232 (47.4)	
Co-trimoxazole use, n (%)			
YES	220 (60.8)	142 (39.2)	<0.001
NO	94 (42.7)	126 (57.3)	
Renal Dysfunction stage, n (%) **			
I= Normal or increased GFR	193 (53.5)	168 (46.5)	0.51
II=Slightly decreased GFR	83 (49.7)	84 (50.3)	
III= Moderately decreased GFR	17 (60.7)	11 (39.3)	
IV= severely decreased GFR	1 (100)	0	
276 participants had missing creatinine results at 18 months and were excluded from this table as creatinine clearance could not be calculated. * Mean (SD) and chi-square test for association † Median (IQR): Two-sample Wilcoxon rank signed test (Mann–Whitney) performed ** 18 months Creatinine clearance after ART initiation			

Table 5: univariate and multivariate analysis of renal function as a binary outcome						
Variable	**OR**	**95% CI**	**Unadjusted P value**	**OR**	**95% CI**	**Adjusted P value**
Baseline creatinine	1.00	0.98-1.02	0.056	1.00	0.99-1.00	0.118
TDF exposure Non TDF	1		1	1		1
TDF	2.52	0.79-8.00	0.118	1.01	0.98-1.04	0.529
Baseline urea	1.13	0.74-1.73	0.568	1.00	0.98-1.01	0.990
Gender						
Female	1		1	1		1
Male	0.61	0.17-2.20	0.453	0.98	0.95-1.02	0.365
Age						
15-34	1		1	1		1
35-49	1.81	0.12-1.57	0.983	0.98	0.95-1.02	0.302
>50	6.35	2.18-18.4	0.001	1.78	1.03-1.92	0.001
Baseline CD4 cell count						
<350	1		1	1		1
350-500	3.03	0.98-9.28	0.053	1.02	0.97-1.07	0.051
>500	0.69	0.08-5.52	0.726	1.00	0.98-1.05	0.974
Baseline weight						
30-49	1		1	1		1
50-69	0.52	0.18-1.46	0.218	0.96	0.93-1.00	0.089
70-80	1.63	0.12-2.85	0.992	0.95	0.89-1.01	0.133
TB medication						
Yes	1		1	1		1
No	1.66	0.55-5.02	0.367	1.02	0.98-1.06	0.221
Predictor variables included in full model: demographics, baseline creatinine, weight, age, TB medication and baseline CD4 cell count. Final model developed by backward selection until all covariance were at P < 0.05 level. OR = Odds ratio, CI = Confidence interval						

Table 6: CD4+cell count difference of renal dysfunction in HIV patients on TDF at 18 months follow up by age categories at Ronald Ross Hospital Zambia				
Group with young patients	**CD4+cell difference**	**Prevalence % (n)**	**aOR (95% CI)**	**p-value**
	≤350	0.56 (177)	Ref	
	>350	4.87 (41)	0.24 (0.06-0.79)	0.011
Group with older patients	≤350	2.34 (171)	Ref	
	>350	7.69 (56)	4.25 (1.26-14.33)	0.019
Notes: 1) Sample size n=429. 2) Those with CrCl <50ml/min at start of treatment were excluded 3) age defined: younger<50yrs and older>50yrs 4) aOR=Adjusted odds ratios				

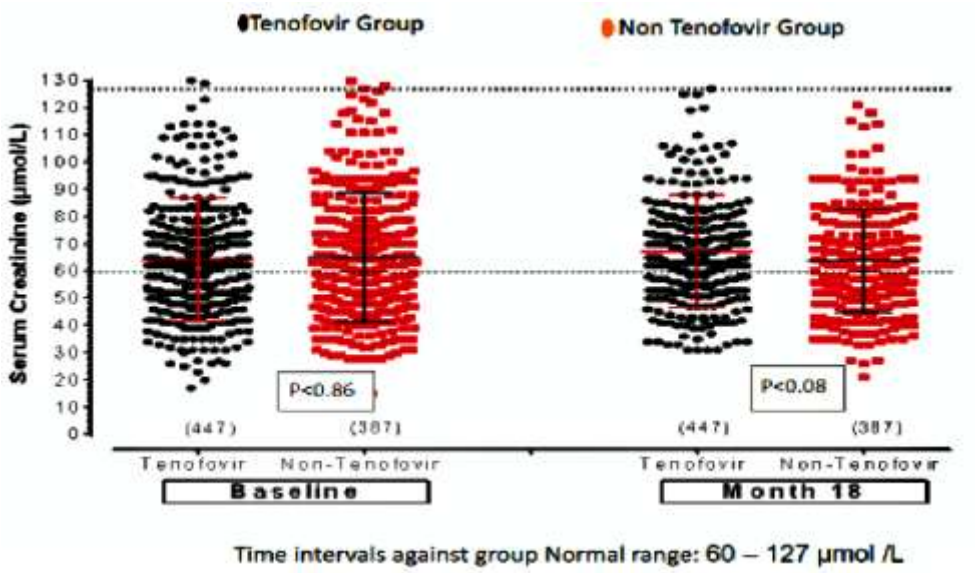

Figure 1: blood creatinine at baseline and month 18

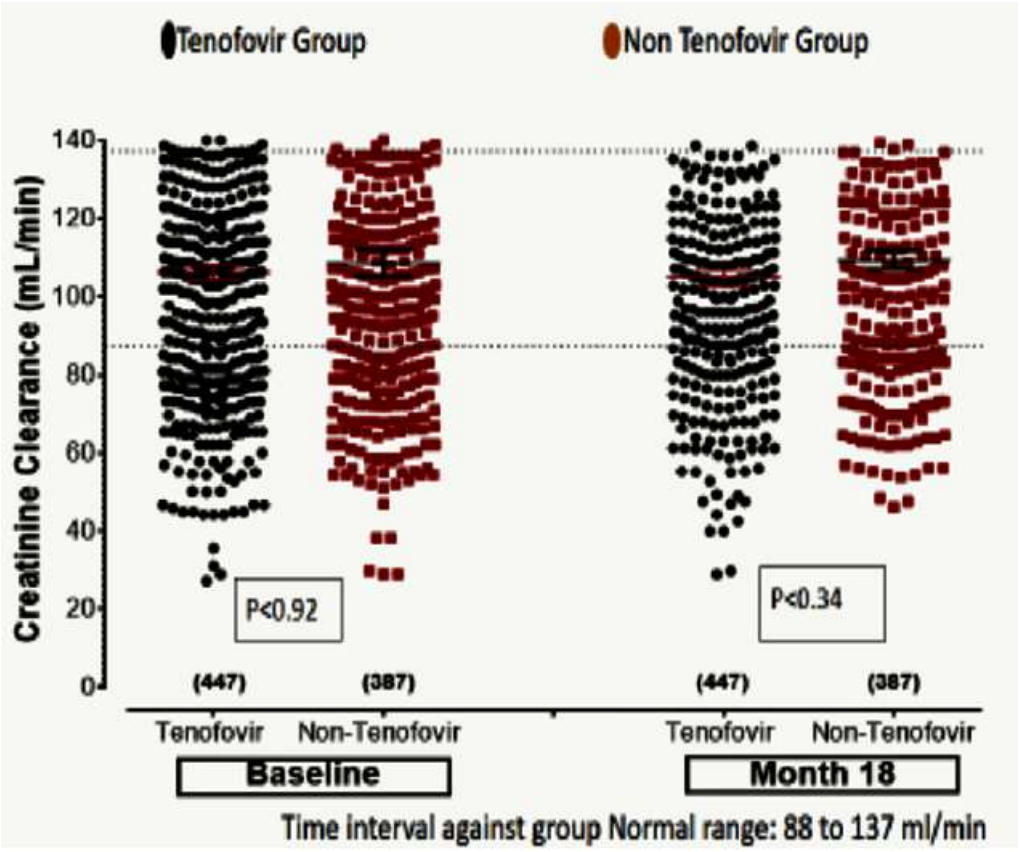

Figure 2: creatinine clearance at baseline and month 18