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RESEARCH ARTICLE

STUDY OF TENOFOVIR NEPHROTOXICITY WHILE COMPARING THE CASES ON TENOFOVIR CONTAINING TLE REGIMEN AND THEIR CONTROLS ON NON- TENOFOVIR CONTAINING ZNL REGIMEN AT A TERTIARY CARE HOSPITAL IN NORTHERN INDIA

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ABSTRACT

Introduction: National AIDS Control Organisation (NACO) recommends either Zidovudine or Tenofovir Disoproxil Fumarate (TDF) as one of the reverse transcriptase inhibitors (RTIs) to be included in the first-line ART regimens- Zidovudine, Nevirapine and Lamivudine regimen (ZNL regimen); and Tenofovir, Lamivudine and Efavirenz regimen (TLE regimen). Tenofovir has been variously documented as a potential agent that can cause nephrotoxicity and bone mineral disease, but, there are conflicting observations about the clear evidence of any Tenofovir-induced nephrotoxicity and related aspects. The current study is aimed to address this issue.

Material and methods: The prospective case-control study was conducted at a NACO and PSACS-approved ART-OPD of Government Medical College & Guru Nanak Dev Hospital, Amritsar on 100 HIV-positive cases, with ages between 18 to 65 years, and with a minimum of more than 6 weeks of duration of treatment; on Tenofovir-based ART (TLE regimen) who were compared with 100 similar HIV-positive patients on non-Tenofovir-based ART (ZNL regimen) serving as their controls. Patients with pre-existing underlying renal disease, diabetes mellitus, hypertension, concomitant use of any nephrotoxic drug, protease inhibitor or steroid therapy for any cause for a duration of more than 3 months were excluded. The cases and controls were compared for age (completed years), duration of treatment with ART (in months), height, weight, BMI, corrected serum calcium, creatinine clearance (estimated using the Cockcroft-Gault equation), CD4 count at initiation of ART, and sex of the study subjects. Renal toxicity TDF was evaluated by tubular proteinuria and reduced creatinine clearance (calculated by Cockcroft-Gault Equation). Data analysis was conducted by using statistical software SPSS Version 16(89) and Excel 10. Statistical significance was evaluated using Students t test and ANOVA.

Results: The comparison of Urine Protein and Creatinine Ratio (UPCR) among cases and controls showed that Odds Ratio was 7.0 (95% CI 1.1 - 50.1) indicating that risk of having an increased UPCR of 0.2 or more was 7 times higher among those HIV-infected patients who were treated with TDF-based ART as compared to those who were treated on non-TDF-based ART.

The analysis of Cr Cl (as estimated by the Cockcroft-Gault equation) among the groups revealed that the cases had significantly lower Cr Cl as compared to controls (Chi Square value: 5.07, p value 0.022).

Subgroup analysis between different treatment duration groups showed that treatment with TDF is provided for 60 months or longer, it would increase UPCR significantly.

Conclusions: Exposure to TDF during treatment of HIV has a role in lowering the creatinine clearance.

INTRODUCTION

HIV-infection has claimed more than 39 million lives. In 2015 alone, global death toll from HIV and HIV-related causes was estimated at 1.1 million. The number of People Living with HIV/ AIDS (PLHA) was approximately 36.7 million by the end of 2015. The number of new case of HIV infection was approximately 3.2 million in 2000, which has come down to an estimated 2.1 million new cases in 2015.[1] Highly Active Antiretroviral Therapy (HAART) is the basis for the global control of the HIV/ AIDS epidemic.

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It has been established that ART is highly effective in improving health and reducing the risk of transmission of HIV, thereby contributing to prolongation of life in HIV/AIDS patients.[2]

Tenofovir is an acyclic nucleotide phosphonate di-ester analog of adenosine monophosphate. It achieves its anti-retroviral action by inhibiting HIV-1 reverse transcriptase activity; this action being achieved by competitive antagonism of de-oxyadenosine 5'-triphosphate. Once Tenofovir is incorporated into the DNA in place of de-oxyadenosine 5'-triphosphate, it causes DNA chain termination. Currently, NACO recommends either Zidovudine or Tenofovir as one of the NRTIs to be included in the first-line ART regimen, in which Tenofovir is included in regimens I (a), II (a), IV and IV (a).[3] There are

multiple reasons for the inclusion of Tenofovir as the preferred NRTI. It has a better safety profile and has the least toxicity, as compared to the other agents in the group. It also lends itself to single dosing, thereby making adherence to therapy easier.

Tenofovir has been variously documented as a potential agent that can cause nephrotoxicity and bone mineral disease. In two phase III trials assessing the effect of Tenofovir on renal parameters, nephrotoxicity was addressed and was defined as an eGFR of less than 50 mL/ min/ 1·73 m².[4] There was no evidence of any Tenofovir-induced nephrotoxicity, although reductions in eGFR of approximately 10% were documented. However, in a few cohorts that were assessed, there was a decrease in the creatinine clearance with the decrease being more than 50% of the baseline values in about 4% of Tenofovir recipients. This reduction in creatinine clearance was observed after a median time of 12 months.[5]

The renal proximal tubule is the main site of Tenofovir toxicity, and it is evident clinically as a small decline in creatinine clearance (CrCl), calculated by using Cockcroft-Gault (CG) formula. In severe cases, the solute transport is affected causing renal Fanconi Syndrome - which includes glycosuria (with normoglycemia), tubular proteinuria, aminoaciduria and uricosuria. Detection of tubular proteinuria, along with assessment of CrCl is a very sensitive method of identifying proximal tubular dysfunction.[6-11] However, data from India and Africa do not feature in this because of a lack of long-term use and research gap. Although, there have been some studies to study the renal toxicity associated with Tenofovir; and even shorter truncated studies and case reports to study the bone mineral disease associated with it; to the best of our knowledge, there is no published Indian data in this context that has assessed the various parameters that may be involved in worsening of renal function and compared those with a control group.

MATERIAL AND METHODS

The study was conducted on 100 HIV-positive patients on Tenofovir-based ART (TLE regimen) with 100 HIV-positive patients on non-Tenofovir-based ART (ZNL regimen) serving as their controls.

Inclusion Criteria (for cases and controls)

1. HIV infected patients on TLE regimen (cases) and ZNL regimen (controls).
2. a minimum of more than 6 weeks of duration of treatment, and
3. between the ages of 18 to 65 years.

Exclusion Criteria (for cases and controls)

1. Patients with pre-existing underlying renal disease,
2. Pre-existing diabetes mellitus,
3. Pre-existing hypertension,
4. Concomitant use of any protease inhibitor, steroids or nephrotoxic drug for more than 3 months,

Renal toxicity of TDF was evaluated by tubular proteinuria and reduced creatinine clearance (calculated by Cockcroft-Gault Equation).

Data analysis was conducted by using statistical software SPSS Version 16(89) and Excel 10. Statistical significance was evaluated using Students t test and ANOVA.

RESULTS

The cases and controls were compared for age (completed years), duration of treatment with ART (in months), height, weight, BMI, corrected serum calcium, creatinine clearance (estimated using the Cockcroft-Gault equation), CD4 count at initiation of ART, and sex of the study subjects. It was observed that the cases and controls were closely comparable on various characteristics and variables relevant to HIV-treatment decision making. The difference in various variables was not found to be statistically significant. Table 1 shows a comparison of cases and controls with respect to values at baseline.

Table No 1 Comparison of Characteristics of Cases (n=100) and Controls (n=100)

Characteristics	Cases	Controls	t value	p value
Number	100	100		
Age (in completed years)	38.24	40.47	-1.35	0.178
Time since ART initiation(months)	64.27	60.37	.520	0.604
Height (cm)	162.83	162.80	-.050	0.960
Weight (kg)	59.44	59.70	-.138	0.889
BMI (kg/m^2)	22.31	22.43	-.208	0.836
Corrected Serum Calcium(mg/dL)	8.75	8.69	.606	0.546
Creatinine Clearance (mL/min)	107.11	106.76	.043	0.966
CD4 count at initiation of ART(cells/ µL)	192. 35	242.17	-1.65	0.372
Sex Male (%)	54	56	2 .165	0.685
Sex Female (%)	50	50		

The comparison of UPCR among cases and controls showed that Odds Ratio was 7.0 (95% CI 1.1 - 50.1) indicating that risk of having an increased UPCR of 0.2 or more was 7 time higher among those HIV-infected patients who were treated with TDF-based ART as compared to those who were treated on non-TDF-based ART. However, the confidence intervals showed side variations. The Chi Square test revealed it to be a statistically significant difference (p value 0.04). Table 2 shows Odds Ratio of UPCR among cases and controls.

Table No 2 Urine Protein and Creatinine Ratio (UPCR) for TDF and Non TDF Based Treatment Regime of HIV Patients [Cases (n=100) and Controls (n=100)]

Urine Protein Creatinine Ratio (UPCR)	Cases (%)	Controls (%)	Total (%)
Less than 0.20	89 (89%)	98(98%)	187 (94%)
0.20 and above	11 (11%)	2 (2%)	13 (6%)
Total	100	100	200
χ^2= 4.224 p value: 0.040			

Odds Ratio (OR) = 7.00; CI, LL 1.1. – UL 50.

The analysis of CrCl (as estimated by the Cockcroft-Gault equation) among the groups revealed that the cases had significantly lower CrCl as compared to controls (Chi Square value: 5.07, p value 0.022). It may be, therefore, considered that exposure to TDF during treatment of HIV has a role in lowering the creatinine clearance. Table 3 show the distribution of creatinine clearance, as estimated by the Cockcroft-Gault equation, among the cases and controls.

Table No 3 Distribution of Creatinine Clearance among Cases (n=100) and Controls (n=100)

Creatinine Clearance (CrCl) (mL/min)	Cases (%)	Controls (%)	Total (%)	Level of Significance
Less than 60	82 (82%)	95 (95%)	177 (88%)	χ^2 5.207
More than 60	18 (18%)	5 (5%)	23 (12%)	p value 0.022
Total	100	100	200	

Simple logistic regression analysis of the factors associated with Urine Protein/Creatinine Ratio (UPCR) was performed. Treatment with TDF among cases, as compared to the controls, was associated with increased UPCR, although the association was not statistically significant. The factors, namely, creatinine clearance of less than 60 mL/min (p value 0.035), and serum creatinine levels more than 2.5 mg (p value 0.005) were found to be associated with higher UPCR levels among cases as compared to controls with a high level of significance. BMI and CD4 counts less than 200 cells/ µL at the initiation of treatment did not show any significant association with UPCR. Table 4 shows the results of simple logistic regression analysis of the factors associated with Urine Protein/Creatinine Ratio (UPCR).

Table No 4 Simple Logistic Regression Analysis of Factors (independent variables) associated with Urine Protein and Creatinine Ratio (UPCR) (dependent variable) among Cases (n=100) and Controls (n=100)

Variables/Risk Factors	β-Coefficient	S.E.	p Value
TDF vs Non-TDF	-1.946	1.085	0.073
CrCl (mL/min) <60 vs 60 or more	1.668	0.791	0.035
Weight (kg) 50 or more vs <50	0.295	1.098	0.788
BMI (kg/m^2) <18.5 vs 18.5 or more	0.019	1.104	0.986
S Creatinine (mg/dL) 2.5 and above vs <2.5	3.664	1.084	0.005
CD4 (cells/ µL) <200 vs 200 or more	-0.579	0.753	0.442
Age (years) <40 vs 40 or more	0.959	0.646	0.071

Multivariate logistic regression analysis of factors (independent variables) related with UPCR (dependent variable) among cases and controls, adjusted for the effect on UPCR, was done. Serum Creatinine was not included in the model as it was found to be closely collinear with the urine Creatinine. All variables were entered in the model as categorical variables simultaneously.

The UPCR was almost significantly associated with TDF-exposure, adjusted for other factors in the regression equation. Effect of TDF on UPCR was independent of the effect of CrCl, BMI, age, weight and CD4 count. The effect of CrCl (p value 0.046) remained significant, and that of age (p value 0.057) was almost significant, and both these factors were independent of the effect of any other variable included in the equation. The results of the multivariate regression concluded that use of TDF, low CrCl and age are significantly associated with UPCR independent of the effect of each other, and other factors as well. Table 5 shows multivariate logistic regression analysis of factors (independent variables) with Urine Protein-Creatinine Ratio (dependent variable) among cases and controls, adjusted for the effect on UPCR.

Table No 5 Multivariate Logistic Regression Analysis of Factors (independent variables) with Urine Protein and Creatinine Ratio (UPCR) (dependent variable) among Cases (n=100) and Controls (n=100)

Variables/Risk Factors	β-Coefficient	S.E.	p Value
Constant	-5.093	1.745	0.004
TDF vs Non-TDF	-1.930	1.131	0.088
CrCl (mL/min) <60 vs 60 or more	2.248	1.124	0.046
Age (years) <40 vs 40 or more	1.332	0.693	0.057
BMI (kg/m^2) <18.5 vs 18.5 or more	-0.402	0.798	0.798
CD4 (cells/µL) <200 vs 200 or more	-0.486	0.895	0.587
Weight (kg) 50 or more vs <50	-1.993	1.787	0.265

The final parsimonious multivariate logistic regression model of factors (independent variables) with UPCR (dependent variable) among cases and controls was performed. The final parsimonious multivariate logistic regression model included only TDF treatment and age of the patients. The results of the analysis showed that treatment with TDF among HIV patient was significantly associated with high UPCR, independent of all other factors. Similarly, age of the patients was also significantly associated with higher UPCR, independent of all other factors, as well as irrespective of whether treated with TDF or not. Table 6 shows final parsimonious multivariate logistic regression model of factors (Independent variables) with Urine Protein-Creatinine Ratio (Dependent variable) among cases and controls.

Table No 6 Multivariate Logistic Regression Analysis: Final Parsimonious Regression Model

Variables/Risk Factors	β-Coefficient	S.E.	p Value
TDF vs Non-TDF	-2.267	1.113	0.042
Age (years) <40 vs >40	1.481	0.698	0.034
Constant	-5.433	1.732	0.002

The subgroup analysis according to age categories and mean UPCR levels among cases and controls revealed that the overall mean UPCR was 0.14 among cases and controls. The mean UPCR was low, 0.11 (SD $\pm$ 0.013) among patients aged less than 40 years as compared to higher mean UPCR level (0.19 SD $\pm$0.013) among patients aged 40 years or more. The analysis showed no statistically significant difference between the groups (t -1.548, p >0.05). Table 7 shows the subgroup analysis according to age categories and mean UPCR levels among cases and controls.

Table No 7 Mean UPCR Levels as per the Age of Cases (n=100) and Controls (n=100)

Age (Years)	Number	Mean UPCR	+ SE	t value	p Value
Less than 40	115	0.11	0.013	-1.548	0.124
More than 40	85	0.19	0.065		
Total	200	0.14	0.027		

Age wise subgroup analysis of mean UPCR levels among cases only was done. Those who were treated with TDF and were 40 years or older had higher mean UPCR levels (0.19 SD $\pm$ 0.143) than the younger patients with TDF, i.e. aged less than 40 years. The difference in mean UPCR levels in the two age groups was statistically significant (t -1.984, p <0.05), mean UPCR being higher in higher age group of TDF treated patients. Table 8 shows the age wise subgroup analysis of mean UPCR levels among cases only.

Table No 8 Mean UPCR Levels According to Age of Cases (n=100) Only

Age (years)	Number of Cases on TDF	Mean UPCR	+ SE	t value	p Value
Less than 40	64	0.09	0.015	-1.984	0.052
40 or more	36	0.19	0.143		

Analysis of Variance (ANOVA) was applied to assess whether the duration/length of treatment with TDF affects the levels of UPCR. The UPCR levels were compared for different durations of treatment with TDF, viz; less than 12 months; 12-60 months, and 60 and more months. The UPCR was significantly associated with the duration/length of treatment with TDF. It was concluded that longer the duration with TDF, higher was UPCR. Table 9 (a) shows the effect of duration/ length of treatment with TDF on UPCR levels.

Table No 9 (a) Analysis of Variance (ANOVA) – Duration of TDF Therapy among Cases (n=100) and UPCR Between and Within Groups

Comparison of Duration of TDF	Mean Square	F	p Value
Between Groups	.521		
Within Groups	.165		
		3.153	0.05
Total			

Multiple Group Between and Inter-group comparisons of duration of treatment with TDF and mean UPCR using ANOVA was also performed. In the analysis, each category of duration was compared with the other two categories of duration of treatment with TDF. It was observed that there was no significant difference in change in UPCR between treatment less than 12 months compared to treatment duration 12-60 months ($p > 0.05$). But the comparison of TDF treatment duration less than 12 months and more than 60 months showed a difference on UPCR levels that was approaching levels of significance (< 0.06). Similar comparison of duration of treatment with TDF on UPCR levels was also made for the category of 13-60 months. It was found that while there was no significant difference in UPCR when compared duration less 12 months, the effect was significant when compared with treatment duration more than 60 months ($p < 0.05$). Final comparison of the duration of TDF treatment category more than 60 months was made with the other two categories of duration. It showed a statistically significant effect on UPCR as compared to TDF treatment duration less than 60 months ($p < 0.05$). In the final analysis, it may be concluded that if the treatment with TDF is provided for 60 months or longer, it would increase Urine Protein Creatinine Ratio significantly.

Table No 9 (b) Multiple Group Between and Inter-group Comparisons of Duration of TDF Treatment and Mean UPCR (ANOVA)

Duration of TDF	Comparison	Mean Difference	+ SE	p Value
Up to 12 months	13 to 60 months	-.060	.141	.904
	More than 60 Months	-.452	.200	.069
13 to 60 months	Up to 12 months	.060	.141	.904
	More than 60 Months	-.392	.164	.052
More than 60 months	Up to 12 months	.452	.200	.069
	13 to 60 months	.392	.164	.052

Table 9 (b) shows the Multiple Group Between and Inter-group comparisons of duration of treatment with TDF and mean UPCR using ANOVA.

DISCUSSION

Our study was aimed to detect the potential harmful adverse effects that can be attributed to the use of Tenofovir in ART. Data was recorded by the means of personalised interviews, and the requisite data was generated by the means of clinical and/ or laboratory evaluation, as and when required.

Our study had a total of 200 participants, who were included after ascertaining the inclusion and exclusion criteria, and thereafter by obtaining written informed consent. Out of the total 200 participants, 128 (64%) were males and 72 (36%) were females. This difference in the selection of the patients was not found to be statistically significant enough to affect our results.

An observational cohort longitudinal study in Western India was done in 2010 to assess TDF-associated renal dysfunction. In this study, 1271 HIV-positive patients were started on TDF-based regime and were followed up. The patients were assigned to either an NNRTI-based regime or to a PI-based regime. Evaluations were done at the baseline and at each subsequent follow-up visit. Parameters assessed included serum creatinine, potassium, phosphorous and evaluation of urine. Creatinine clearance was calculated using the Cockcroft-Gault formula. Renal dysfunction was defined as an elevation in serum creatinine to values more than 1.2 mg/dL.[12] This study, however, studied only the outcomes. The authors have mentioned the presence of other risk factors for renal dysfunction in their cohort, but they have not clarified how these factors were accounted for, and what was the effect of these factors on the renal dysfunction. Further, there was no control group to compare the worsening of renal function with, and it is not clear why this worsening was assigned to the use of TDF alone. Also, the quantification of proteinuria was semi-quantitative, based on the results of the urine dip-stick and there was no co-relation of the presence of proteinuria with renal dysfunction; it is also difficult to see how this could have been ascribed to the use of TDF alone.

Our study has fewer patients but may still be considered superior to this study because we have performed a case-control study and have studied various factors that have been discussed earlier. We have focused on the multiple factors contributing to measured proteinuria, their interaction and how they independently affect renal function. By comparing a group of cases with comparable controls, we have attempted to take care of some of the known and possibly a few unknown confounding factors.

The comparison of UPCR among cases and controls showed that Odds Ratio was 7.0 (95% CI 1.1 - 50.1), indicating that risk of having an increased UPCR of 0.2 or more was 7 time higher among those HIV-infected patients who were treated with TDF-based ART (TLE regimen) as compared to those who were on non-TDF-based ART (ZNL regimen). However, the confidence intervals showed side variations. In absolute numbers, our study found that 11% of patients on TDF-based ART (TLE regimen) had elevated UPCR, as compared to 2% of the controls on non TDF based ART (ZNL regimen). Chadwick *et al*[13] had performed a single-centre cross sectional study in Ghana in which they assessed 330 HIV-positive patients out of which 101 were on TDF. The prevalence of dipstick proteinuria among this group was 37% and that of tubular dysfunction was 15%. This value of 15% tubular dysfunction closely approximates our result of 11% prevalence of elevated UPCR in patients on therapy with TDF. In another study by Scherzer *et al*[14] yearly increase in the risk of developing proteinuria was found to be 34% in patients on TDF.

Our data analysis revealed that the cases had significantly lower Cr Cl as compared to controls (Chi Square value: 5.07, p value 0.022). With all other factors being similar and the two groups being comparable to each other, it may be considered with reasonable certainty that exposure to TDF during treatment of HIV has a role in lowering the creatinine clearance. This was observed in our study and was found to be statistically significant. This is similar to the results obtained

by Nishijima *et al*,[15] when they evaluated 792 treatment-naïve HIV-positive patients by dividing them into TDF-based or abacavir-based ART recipient groups and then performed various measures directed at assessing renal function. They estimated the eGFR to determine renal dysfunction, and eGFR was calculated using the Japanese equation developed by the Japanese Society of Nephrology (JSN). They found evidence of renal dysfunction in the Tenofovir-based treatment group when compared to the abacavir-based group, with the loss in eGFR increasing continuously for a period of 5 years.[16]

Simple logistic regression analysis of independent variables associated with the dependent variable (UPCR), among the cases and controls was done. Creatinine clearance of less than 60 mL/min (p value 0.035), and serum creatinine levels more than 2.5 mg/dL (p value 0.005) were found to be associated with higher UPCR levels among cases as compared to controls with a high level of significance.

Multivariate logistic regression analysis of factors related with UPCR was done. CrCl (p value 0.046) remained significant, and age (more than 40 years) (p value 0.057) was almost significant, and both these factors were independent of the effect of any other variable included in the equation. The results of the multivariate regression concluded that use of TDF, low CrCl and age appear to be significantly associated with UPCR independent of the effect of each other, and other factors as well. To the best of our knowledge, similar studies that have evaluated the association of these factors with UPCR are lacking.

This was followed by a final parsimonious regression model with multivariate logistic regression analysis which showed that treatment with TDF among HIV patient was significantly associated with high UPCR, independent of all other factors. Similarly, age of the patients (age more than 40 years) was also significantly associated with higher UPCR, independent of all other factors, as well as irrespective of whether treated with TDF or not.

Multiple Group Between and Inter-group comparisons of duration of treatment with TDF and mean UPCR using ANOVA was also performed. Final comparison of the duration of TDF treatment category more than 60 months was made with the other two categories of duration (up to 12 months, 13-60 months). It showed a statistically significant effect on UPCR as compared to TDF treatment duration less than 60 months ($p < 0.05$). In the final analysis, it may be concluded that if treatment with TDF is provided for 60 months or longer, it would increase UPCR significantly. Various studies have found differing durations of treatment with TDF that affect renal function [12 months- Gallant *et al*[4]] , but none of them, to our knowledge, have made any association between the duration of therapy with TDF and the onset of proteinuria. In the study by Zachor *et al*[17] it was seen that for every 10-year increase in age and for every eGFR value that was 10 mL/min lower at the baseline, the chances of developing RKFD amplified by approximately 70% and 57% correspondingly. Also, each 10-year older age was found to have an association with at least a 1.90-fold amplified risk of evolving stage 3 CKD; but there was no association documented with proteinuria.

The strength of our study lies in the fact that we have applied stringent inclusion and exclusion criteria to choose patients who reflect the group that we are interested in evaluating. We had used well-matched cases and controls to try and weed out both known and unknown confounding factors in the study.

CONCLUSIONS

Our study is one of the first case-control studies from Northern India on this matter. The findings bring to light some interesting questions regarding the use of Tenofovir-based therapy in the management of HIV-infection. The first fact is that there is a significant decrease in the creatinine clearance in the patients on Tenofovir, as compared to the other group (that is not on Tenofovir-based ART), and this toxicity is manifested by an increase in the urine protein to creatinine ratio. Therefore, assessment of UPCR appears to be a good screening method for evaluating Tenofovir-induced renal damage, and appears to be useful in predicting a fall in the creatinine clearance. The second important aspect that the study revealed was the association of increased age (40 years or more) with higher UPCR, which was independent of all other variables. This brings up a very important question- should any age-based cut-off be used to start therapy with Tenofovir to ensure that the effects on UPCR, and by extension Tenofovir-induced nephrotoxicity, should be minimal? Third important aspect brought forward by the study was the effect of duration of therapy (more than 60 months) with TDF on the development of elevated UPCR and thereby onset of renal dysfunction. This is also an important aspect of the profile with the drug that will need consideration once HAART has been initiated and therapy continued for more than 60 months.

It can be concluded, therefore, that any patient on a TDF-based regimen should be monitored for renal dysfunction more closely after 5 years of therapy. In this respect, measurement of UPCR appears to be one of the better modalities to ascertain TDF-induced renal dysfunction. Also, this close monitoring for nephrotoxicity is more relevant in the older patients on TDF.

Unfortunately, not many studies have been done to target these areas and focus on these specific questions; and our study was not powered at the outset to answer these questions. But it has opened a new horizon of further study that can guide further research into the topic in this direction, and thereby help us manage the emerging aspects of HIV-infection in a more holistic manner.

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References

1. UNAIDS. Know your epidemic: AIDS by the Numbers. 2015. p. 28.
2. Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, *et al*. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418.
3. NACO. Guidelines on First-line ART For Adults and Adolescents. 2013.

4. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with Tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clinical Infectious Diseases*. 2005;40(8):1194-8.
5. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, *et al*. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New England Journal of Medicine*. 2006;354(3):251-60.
6. Woodward C, Hall A, Williams I, Madge S, Copas A, Nair D, *et al*. Tenofovir- associated renal and bone toxicity. *HIV medicine*. 2009;10(8):482-7.
7. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney international*. 2010;78(11):1171-7.
8. Calza L, Trapani F, Tedeschi S, Piergentili B, Manfredi R, Colangeli V, *et al*. Tenofovir-induced renal toxicity in 324 HIV-infected, antiretroviral-naive patients. *Scandinavian journal of infectious diseases*. 2011;43(8):656-60.
9. Fauci A, Lane HC. Human Immunodeficiency Virus Disease: AIDS and Related Disorders. In: Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J, editors. Harrison Pricnciples of Internal Medicine, 19th ed. United States of America. McGraw-Hill. 2015;19:1278.
10. Verhelst D, Monge M, Meynard JL, Fouqueray B, Mougenot B, Girard PM, *et al*. Fanconi syndrome and renal failure induced by Tenofovir: a first case report. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2002;40(6):1331-3.
11. Schaaf B, Aries SP, Kramme E, Steinhoff J, Dalhoff K. Acute renal failure associated with Tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2003;37(3):e41-3.
12. Patel KK, Patel AK, Ranjan RR, Patel AR, Patel JK. Tenofovir-associated renal dysfunction in clinical practice: An observational cohort from western India. *Indian Journal of Sexually Transmitted Diseases and AIDS*. 2010;31(1):30.
13. Chadwick DR, Sarfo FS, Kirk ESM, Owusu D, Bedu-Addo G, Parris V, *et al*. Tenofovir is associated with increased tubular proteinuria and asymptomatic renal dysfunction in Ghana. BMC Nephrologu. 2015; 16(1):195
14. Scherzer R, Estrella M, Yongmei L, Deeks SG, Grunfeld C, Shlipak MG. Association of Tenofovir exposure with kidney disease risk in HIV infection. AIDS (London, England). 2012;26(7):867.
15. Nishijima T, Gatanaga H, Komatsu H, Tsukada K, Shimbo T, Aoki T, *et al*. Renal function declines more in Tenofovir- than abacavir-based antiretroviral therapy in low-body weight treatment-naive patients with HIV infection. PloS one. 2012;7(1):e29977.
16. Nishijima T, Kawasaki Y, Tanaka N, Mizushima D, Aoki T, Watanabe K, *et al*. Long-term exposure to Tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS*. 2017;28(13):1903-10.
17. Zachor H, Machekano R, Estrella MM, Veldkamp PJ, Zeier MD, Uthman OA, *et al*. Incidence of stage 3 chronic kidney disease and progression on Tenofovir-based regimens. *AIDS*. 2016;30(8):1221-8.

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