Is the risk of tenofovir-induced nephrotoxicity similar in treatment-naïve compared to treatment-experienced patients?

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Abstract

Background: Tenofovir disoproxil fumarate (TDF) is the recommended first line nucleoside reverse transcriptase inhibitor (NRTI) in the management of HIV however its use is associated with nephrotoxicity.

Aim: To assess if the risks of renal impairment was similar in treatment-naïve compared to treatment-experienced patients initiating tenofovir given their different background clinical characteristics.

Method: This was a retrospective observational study conducted at the University Malaya Medical Centre, Malaysia and included all HIV-infected adults who received tenofovir for at least 3 months and had an eGFR >60 ml/min at tenofovir initiation. The incidence of renal impairment was defined as a 25% decrease in eGFR from baseline or the development of chronic kidney disease. Clinical and demographic characteristics were extracted from medical records. Risk factors associated with tenofovir-induced renal impairment were determined using multivariate logistic regression.

Results: This study included 314 patients and almost half of them (49%) were treatment-naïve at tenofovir initiation. The majority of patients were males (89.5%) with a median [interquartile range (IQR)] baseline creatinine clearance of 99.1(85.0-114.0)mL/min). Thirty (9.4%) patients developed tenofovir-induced renal impairment and the incidence rate was higher in treatment-experienced vs treatment-naïve patients (7.0 vs 3.3 cases/100person years, $p=0.049$). Risk factors associated with tenofovir-induced nephrotoxicity in multivariate analysis were older age ($p=0.001$), anaemia ($p=0.027$), concurrent hypertension ($p=0.014$) and higher baseline eGFR ($p=0.007$).

Conclusion: Treatment-experience was not an independent risk factor but rather confounded by multiple characteristics associated with an increased risk of TDF-induced nephrotoxicity. Monitoring all patients presenting with these risks regardless of treatment experience is crucial.

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Introduction

Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor (NRTI) recommended as a preferred first-line NRTI in the recent WHO Consolidated antiretroviral (ARV) guidelines for the management of HIV.¹ TDF exposure however, has been associated with multiple renal complications including acute tubular necrosis, nephrogenic diabetes insipidus, Fanconi Syndrome and a decline in glomerular filtration rate.^{2,3} The reported prevalence of TDF-induced nephrotoxicity in HIV cohorts is widely variable (ranging from 2.4% -19.6%).^{2, 4-10} Additionally, studies from Asian cohorts (Thai, Japanese and India) have tended to report a higher incidence (about 20%) compared to studies in Caucasian cohorts (<5%).^{5-9,11} These differences may be due to differing patient and clinical characteristics as well as differences in definitions used to assess TDF-induced renal impairment.

Numerous factors have been described to influence the development of TDF-induced nephrotoxicity including old age, low body mass index, pre-existing renal impairment at TDF initiation, underlying hypertension and diabetes mellitus, female sex and the concurrent use of nephrotoxic drugs.^{5, 8, 12-14} Additionally, HIV-related risk factors including low baseline CD4 T-cell counts and concurrent use of ritonavir-boosted protease inhibitor have also been associated with the development of TDF-induced renal impairment.^{8,15}

The recent WHO Consolidated ARV guidelines have recommended the use of TDF-containing regimens as first line therapy for HIV infection and to gradually phase out the use of older nucleoside reverse transcriptase inhibitors (NRTIs) including stavudine which is still widely used in many developing countries primarily due to its low cost.¹ Many developing countries including Malaysia have since adopted the WHO recommendations and have introduced programs to switch patients from older NRTIs to tenofovir-based regimens as well as use TDF-containing regimens as first-line therapy in treatment-naïve patients.¹ Data from prior published studies however, have not been clear if there are differences in risks of TDF-induced nephrotoxicity in these two groups given that their clinical characteristics are likely to be different at TDF initiation. Treatment-experienced patients switching to TDF-containing regimens are likely to be older, have had longer ART exposure and experience less immunodeficiency at the time of TDF initiation. Treatment-naïve patients initiating ART with TDF-containing regimen on the other hand are likely to have advanced

immunodeficiency with multiple opportunistic infections, high levels of immune activation and low body weight at TDF initiation.

Therefore our aim in this study was 1) to compare the incidence of TDF-induced renal impairment in treatment-naïve patients initiating TDF compared to treatment-experienced individuals switching to TDF-containing regimens and 2) to assess if initiating TDF in either of this setting is an independent risk factor associated with TDF-induced renal impairment in a clinic-based cohort.

Method

Study population and design

This was a retrospective observational study among HIV-infected patients attending the Infectious Disease Clinic in University Malaya Medical Centre (UMMC), Malaysia. All patients receiving tenofovir (TDF) since its introduction in the hospital formulary in January 2009 till the study initiation in July 2014 were identified from pharmacy records. Patient medical records were then reviewed for the following inclusion criteria; 1) Patients receiving standard dose tenofovir (300mg once daily) for at least 3 months as part of a combination antiretroviral regimen, 2) at least one serum creatinine measurement done within 6 months before the initiation of TDF and 3) patients with an estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73m² at TDF initiation. In addition, patients who did not have renal function monitored or loss of follow up after starting TDF were excluded from the study. Foreigners were excluded to avoid any ambiguity from the irregular assessment of renal function as the costs for laboratory tests are not subsidised in these patients and often prohibitively high. Serum creatinine was measured by the hospital's central diagnostic lab using an enzymatic colorimetric assay.

Data collected and definitions

In patients fulfilling the inclusion criteria, demographic, clinical and laboratory data at ART and TDF initiation (baseline) and during follow-up were extracted from medical records. Patients who were treatment naïve were individuals with no previous records of receiving any ART. Underlying comorbidities including diabetes, hypertension and dyslipidemia were recorded if previously diagnosed by a physician and noted in the medical case notes. Anemia was defined as haemoglobin concentrations <130g/L in males and <120g/L in females while the presence of chronic hepatitis C and B were defined as the presence of anti-HCV

antibodies and the presence of hepatitis B surface antigens, respectively. The study was approved by the hospitals ethics review board (MEC 1031.102).

Main outcome measures

The end-points of this study were TDF-induced nephrotoxicity defined as a 25% decrease in at least one eGFR measure from TDF initiation (baseline) or the development of chronic kidney disease (CKD) which was defined as $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ on consecutive measures for at least 3 months.¹⁶ eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.^{17,18} In patients who did not achieve the study end-points, observations were censored when tenofovir was discontinued for reasons other than renal impairment, referred to other health care facilities or till the last available follow-up date. Baseline eGFR was calculated using serum creatinine concentrations measured within 6 months prior to TDF initiation.

Statistical analysis

eGFR measurements at every 3-6 months following TDF initiation was used to determine the trend of eGFR change during follow-up and was compared to baseline eGFR using Wilcoxon signed rank test. Risk factors associated with TDF-induced renal impairment were determined using multivariable logistic regression. Predictor variables for the multivariable model were selected based on comparison between methods of forward selection and backward elimination. The a priori assumption was that variables with a $p < 0.25$ in the univariable model were candidates predictors to be included in the multivariable model where a p-value of < 0.05 was considered significant. All statistical analysis was performed using IBM SPSS 20 and Stata SE 11.

Results

Five hundred and fifty patients received tenofovir (TDF)-containing ART regimens for at least 3 months from January 2009 till July 2014. Following chart review, a total of 236 patients were excluded for various reasons (Figure 1). A total of 314 patients were included in the final analysis.

A) Cohort characteristics

The majority of the patients in the study were Chinese (58.3%) males (89.5%) with a median (interquartile range, IQR) age of 38 (32-46) years. The baseline characteristics of the study cohort are summarized in Table 1.

At TDF initiation, the median (IQR) eGFR and CD4 T-cell counts were 99.1(85.0-114.0) mL/min/1.73m² and 263(89-447) cells/μL, respectively. However, one-third of the cohort had mild renal impairment (defined as eGFR 60-89 mL/min/1.73m²) which is not a contraindication for TDF initiation. Almost half of the cohort (49%) was treatment-naïve when TDF was initiated. The overall median (IQR) duration receiving TDF was 18.0 (11.0-28.0) months with 1.9% of patients receiving TDF for >5 years.

B) Incidence of tenofovir-induced nephrotoxicity in treatment-naïve vs treatment experienced patients

Thirty (9.6%) patients developed renal impairment following TDF initiation with an incidence rate of 5.4 cases per 100 person-years [95% confidence interval (CI): 3.8-7.6 cases per 100 person-years]. The median (IQR) time from commencement of TDF to the development of TDF-induced nephrotoxicity was 15.0 (10.8-22.8) months. The earliest evidence of TDF-induced renal impairment was 5 months while the latest was 59 months after commencement of TDF. Of the 30 who developed TDF-induced renal impairment, 10 (33.3%) experienced CKD while 20 (66.6%) experienced ≥25% decline in renal function.

The majority of patients who developed TDF-induced nephrotoxicity were treatment-experienced at TDF initiation (73.3%) with the incidence rate significantly higher compared to ART naïve patients receiving TDF [7.0 cases/100 person-years, 95% CI (4.7-10.5) cases/100 person years vs 3.3 cases/100 person years, 95% CI (1.7-6.5) cases/100 person-years, p=0.049]. Treatment-experienced patients when compared to treatment-naïve patients, were found to be older at TDF initiation (40 vs 34 years, p<0.001), receiving TDF for a longer duration (20.0 vs 16.0 months, p=0.006) and had lower nadir CD4 T-cells counts (68 vs 120 cells/μL, p=0.003). In addition, they were also more likely to be hypertensive (17.5% vs 7.8%, p=0.010), have dyslipidaemia (66.3% vs 51.3%, p=0.002), been exposed to ritonavir-boosted PI-based regimen (19.4% vs 1.9%, p<0.001) and experienced mild renal impairment at TDF initiation (36.3% vs 25.3%, p=0.036).

C) Trajectory of decline in renal function following tenofovir-induced renal impairment

When the trajectory of eGFR decline was assessed in the cohort, the earliest pronounced decline in eGFR compared to those not experiencing renal impairment was observed at 3 months followed by 18 months and 36 months after TDF initiation (Figure 2A). There was however, no significant difference in the trajectory of renal function decline when comparing patients who were treatment-experienced versus treatment-naïve at TDF initiation (Figure 2B).

D) Risk factors associated with tenofovir-induced nephrotoxicity

We next assessed risk factors associated with TDF-induced renal impairment using logistic regression. In univariable analysis, increased TDF-induced renal impairment was significantly higher in patients who were treatment-experienced when initiating TDF vs treatment-naïve ($p=0.013$). In addition, older age ($p<0.001$), lower body weight ($p=0.029$), concurrent hypertension ($p<0.001$) and anaemia ($p=0.026$) were also significantly associated with increased risk of TDF-induced renal dysfunction in the univariable analysis.

In multivariable logistic regression, we found increased age ($p=0.001$), concurrent anaemia ($p=0.027$), concurrent hypertension ($p=0.014$) and increased baseline eGFR ($p=0.007$) to be independently associated with TDF-induced renal impairment. Treatment-experienced at TDF initiation and low body weight were no longer significantly associated with TDF-induced renal impairment in the multivariable model (Model 1 in Table 2).

The decline of renal function may be a slow insidious process and not immediately apparent clinically by observed eGFR values. Thus we excluded patients with a history of AKI, mild renal impairment and exposure to nephrotoxic drugs ($n=171$) and performed a re-analysis in a subset of the patients. In this analysis (Model 2 in Table 2), increased age ($p=0.001$), concurrent hypertension ($p=0.020$) and increased baseline eGFR ($p=0.007$) remained independently associated with TDF-induced renal impairment (Table 2) while anaemia was no longer a risk factor.

Discussion

In this clinic-based cohort from a large tertiary care hospital in Malaysia, we found TDF-induced renal impairment was 9.6% with an incidence rate of 5.4 cases per 100 person-years. We also found the incidence rate for TDF-induced renal impairment to be significantly higher in treatment-experienced patients switching to TDF-based regimen from older NRTI-based ART (7.0 cases per 100 person-years) compared to treatment-naïve individuals initiating treatment with TDF-based regimen (3.3 cases per 100 person-years). In multivariable

analysis, we found older age, concurrent hypertension, higher median eGFR at TDF initiation and anemia to be independent risk factors associated with TDF-induced renal dysfunction. Treatment-experienced patients had more confounding risk factors associated with TDF-induced renal impairment and the higher incidence rate in these patients was not an independent effect of prior treatment.

The prevalence of TDF-induced renal impairment is highly variable ranging from 2.4%-19.6% depending on the study location, cohort characteristics and definition of nephrotoxicity used.^{2,4,5-10} The incidence rate of TDF-associated nephrotoxicity in our study was lower compared to rates in other Asian settings including Thailand and Japan which used similar study endpoint definitions (range 10.5-16.2 per 100 person-years).^{5,8} The reasons for these differences are not entirely clear but could be due to differences in patient characteristics. Of note, the study conducted in Thailand, had a higher proportion of females (43.2% vs 10.5%) and in both the Thai and Japanese cohorts, there was much larger proportion of patients receiving concurrent PIs compared to ours (29.1% - 89.4% vs 10.8%), both of which are established risk factors for the development of TDF-induced renal impairment.^{5,13,19}

We also found that the incidence rate of TDF-induced renal impairment in treatment-experienced individuals was more than two-fold higher compared to treatment-naïve patients initiating TDF-containing ART regimens. Despite the higher incidence rate among treatment-experienced patients, we did not find treatment-experience to be an independent risk factor associated with TDF-induced renal impairment in the multivariable analysis. Additionally, trajectories of eGFR decline was also not different in treatment-experienced vs treatment-naïve patients implying that while the incidence rate of renal impairment was different, this may have been driven by other confounding factors. Indeed, treatment-experienced patients initiating TDF were more likely to be hypertensive and older, two risk factors found to be associated with TDF-induced renal impairment in our cohort as well as other studies.^{8,15,20} Additionally, treatment-experienced individuals had lower CD4 T-cell nadir, greater exposure to PI-based regimens, longer duration on ART and a higher proportion had mild renal impairment at TDF initiation; characteristics which are consistent with a long ART treatment history and incidentally also associated with increased risks of TDF-induced renal impairment.^{15,20,21} Therefore treatment-experienced individuals may inherently have multiple characteristics that predisposes them to TDF-induced renal impairment compared to ART naïve individuals initiating TDF. A limited number of studies

to date have assessed the role of treatment-experience and TDF-induced renal impairment.^{5,8} We felt addressing this question was of clinical importance especially in a developing country setting where efforts to switch individuals from older NRTIs to TDF-containing regimens are likely to increase in the coming years as more countries incorporate recommendations from the recent WHO treatment guidelines into local treatment protocols.

We additionally found individuals who were anaemic (haemoglobin concentrations < 130g/L in males and 120g/L in females) at initiation of TDF to be at increased risk of renal impairment however anaemia was no longer significant in a subset analysis when individuals with mild renal impairment or those taking nephrotoxic drugs which included trimethoprim-sulphamethoxazole were excluded. A quarter of our cohort were anaemic at TDF initiation and a third of them switched to TDF due to severe anaemia secondary to zidovudine. Close to 40% of the cohort was also receiving trimethoprim-sulphamethoxazole at TDF initiation which has known myelosuppressive effects. Given that anaemia was no longer significant after exclusion of patients with mild renal impairment would imply that anaemia secondary to erythropoietin deficiency may have been a potential cause. A recent study in an African cohort has also reported an association between anaemia and TDF-induced renal impairment.²² The mechanism of how anaemia may increase TDF-induced renal impairment is currently unclear and needs to be studied further.

Prior studies found low baseline renal function to be an important risk factor associated with increased TDF-induced renal impairment.^{2,20} We however found a paradoxical association of high baseline eGFR to be associated with an increased risk of TDF-induced nephrotoxicity. Numerous studies, some of which have used similar study end-point definitions, have also reported a similar paradoxical association and the odds ratio found in our study of 1.22 was within the range of those reported previously (1.10-1.62).^{2,5,8} As speculated in these other studies, this finding could be due to the difficulty in proving a further decrease in eGFR in patients who already had a low eGFR at baseline. However, the exact reason for this association is unknown and could potentially be influenced by unmeasured confounders.

Low body weight was not an independent risk factor associated with TDF-induced nephrotoxicity in our study compared to other Asian studies though the median weight of patients in our study was somewhat comparable (62.3 kg vs 56.5-63.0 kg).^{5,8,23} This could potentially be due to insufficient patient numbers as a significant association was seen but

only at a univariable level. Additionally, an assessment of body mass index or lean body mass which better reflects overall TDF exposure would have been more accurate in this context but were not routinely measured in patients and we therefore could not assess these parameters in our cohort.²⁴

There were a number of important limitations to our study. Firstly, this was a retrospective observational study and therefore our findings might be influenced by unmeasured confounding factors. Secondly, we only assessed renal function using serum creatinine and may have missed TDF-induced tubular toxicities which require more detailed laboratory assessments for diagnosis. Urinalysis and serum electrolytes are however not routinely performed in our setting and this therefore precluded us from including tubular toxicities as an end-point in our study. Our study may therefore have underestimated the incidence of TDF-induced renal impairment. Thirdly, we included patients with an eGFR of at least 60 ml/min and our threshold for defining CKD was set at a threshold of <60 ml/min for at least 3 months which meant that a small decrease in eGFR for an individual at the low end threshold of the inclusion criteria would have classified them as having CKD. We did not set the threshold for the inclusion criteria to be higher as we wanted to explore in our models if individuals presenting with mild renal impairment (defined as eGFR between 60-89 ml/min) were also at an increased risk of TDF-induced nephrotoxicity, a question still unclear from the current literature. Additionally, of the 10 patients who were classified as having CKD using this definition, we found only one patient who was at the low end of this range (reporting eGFR of 63 ml/min). The median baseline eGFR in this group was 88 ml/min while the calculated average decline from baseline to reach a threshold of 60 ml/min was also quite large, 25 ml/min (min 3ml/min, max 62ml/min). Thus, we do not feel that the current thresholds set for the inclusion criteria and to define CKD would have overly biased our classification of patients as having CKD in this study. Lastly, although we had screened all patients who received TDF since the drug was included in the hospital formulary in 2009, the number of patients analysed in our cohort was smaller than most other recently published studies on TDF-induced renal impairment. This smaller sample size may have influenced our inability to show statistical significance for some of the more established risk factors for TDF-induced renal impairment in our cohort including low body weight, concurrent use of ritonavir-boosted PI and nephrotoxic drugs.^{5,15,20,25}

301 In conclusion, in this study which assessed TDF use in a single tertiary centre, we found the
 302 prevalence of TDF-induced nephrotoxicity to be lower than previously reported in other
 303 centres in the region. Compared to treatment-naïve individuals, the incidence rate of TDF-
 304 induced renal impairment was higher in treatment-experienced patients but this was
 305 influenced by a higher prevalence of confounding risk factors associated with TDF-induced
 306 renal impairment in this group and not due to an independent effect of prior treatment.

307 **Table 1: Clinical characteristics of the cohort and comparisons among those who were**
 308 **treatment-naïve vs treatment-experienced at tenofovir initiation.**

Characteristic	Total	Treatment - Experienced	Treatment- Naïve	p-Value
Patients, n (%)	314	160 (51)	154 (49)	
Demographics				
Ethnicity, n (%)				0.035*
Malay	93 (29.6)	37 (23.1)	56 (36.4)	
Chinese	183 (58.3)	101 (63.1)	82 (53.2)	
Indian	38 (12.1)	22 (13.8)	16 (10.4)	
Median (IQR) age, years	38.0 (32.0-46.0)	40.0 (36.0-47.8)	34.0 (30.0-43.0)	<0.001†
Female gender, n (%)	33 (10.5)	28 (17.5)	5 (3.2)	<0.001*
Median body weight (IQR), kg	62.3 (55.8-69.9)	61.7 (56.0-67.2)	63.5 (55.3-72.1)	0.086†
Underlying comorbidities, n (%)	73 (23.2)	43 (26.9)	30 (19.5)	0.121*
Diabetes mellitus, n (%)	26 (8.3)	18 (11.3)	8 (5.2)	0.052*
Hypertension, n (%)	40 (12.7)	28 (17.5)	12 (7.8)	0.010*
Hepatitis B co-infection, n (%)	19 (6.1)	5 (3.1)	14 (9.1)	0.027*
Hepatitis C co-infection, n (%)	5 (1.6)	4 (2.5)	1 (0.6)	0.190*
Dyslipidaemia, n (%)	185 (58.9)	106 (66.3)	79 (51.3)	0.002*
Liver impairment, n (%)	25 (8.0)	15 (9.4)	10 (6.5)	0.363*
Anaemia, n (%)	81 (25.8)	37 (23.1)	44 (28.6)	0.241*
Concurrent nephrotoxic drug, n (%)	139 (44.3)	68 (42.5)	71 (46.1)	0.520*
ACEI/ARB, n (%)	12 (3.8)	9 (5.6)	3 (1.9)	0.089*
TMP-SMX, n (%)	122 (38.9)	55 (34.4)	67 (43.5)	0.097*
NSAIDS, n (%)	10 (3.2)	8 (5.0)	2 (1.3)	0.062*
HIV status				
Previous history of AIDS-	191 (60.8)	105 (65.6)	86 (55.8)	0.076*

defining illness, n (%)				
Median (IQR) nadir CD4 T-cell counts, cells/ μ L	90 (25-259)	68 (19-228)	120 (39-288)	0.003†
Median (IQR) CD4 T- cell counts at the start of TDF, cells/ μ L	263 (89-447)	393 (168-575)	177 (53-307)	<0.001†
Median (IQR) Log HIV RNA at the start of TDF	4.33 (1.30-5.20)	1.30 (1.30-1.92)	5.14 (4.56-5.55)	<0.001†
ART				<0.001*
NNRTI-based regimen, n (%)	278 (88.5)	127 (79.4)	151 (98.1)	
PI/r-based regimen, n (%)	34 (10.8)	31 (19.4)	3 (1.9)	
Integrase inhibitor, n (%)	2 (0.6)	2 (1.3)	0	
Median (IQR) duration on TDF, months	18.0 (11.0-28.0)	20.0 (12.0-32.0)	16.0 (10.0-25.0)	0.006†
Renal function at TDF initiation				
Median (IQR) SCr, μ mol/L	76.0 (66.0-86.0)	75.5 (65.0-85.0)	77.0 (68.0-87.3)	0.145†
Median (IQR) eGFR, mL/min/1.73m ²	99.1(85.0-114.0)	99.0 (84.2-113.0)	99.2 (86.6-114.0)	0.554†
History of AKI before TDF initiation, n (%)	10 (3.2)	6 (3.8)	4 (2.6)	0.561*
Mild renal impairment, n (%)	97 (30.9)	58 (36.3)	39 (25.3)	0.036*
Other Clinical Parameters at TDF initiation				
Median (IQR) haemoglobin, g/L	137 (116-151)	139 (120-151)	134 (114-151)	0.349†
Median (IQR) ALT, IU/L	37.0 (27.0-55.0)	37.0 (26.5-55.0)	37.0 (27.0-54.8)	0.965†
Median (IQR) AST, IU/L	28.0 (22.0-40.5)	26 (19.0-38.0)	29.5 (23.0-45.0)	0.025†
Social History				
Smoking, n (%)	98 (31.2)	53 (33.1)	45 (29.2)	0.382*
Alcohol consumption, n (%)	109 (34.7)	49 (30.6)	60 (39.0)	0.148*

309 * analysed by Chi-square test

310 † analysed by Mann-Whitney U test

‡Abbreviations: ACEI: angiotensin-converting enzyme inhibitors; AIDS: acquired immune-deficiency syndrome; AKI: acute kidney injury; ALT: alanine transaminase; ARB: angiotensin-receptor blocker; ART: anti-retroviral therapy; AST: aspartate transaminase; eGFR: estimated glomerulus filtration rate; ART: antiretroviral therapy; HIV: human immune-deficiency virus; IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitors; NSAIDS: non-steroidal anti-inflammatory drugs; PI/r: ritonavir boosted-protease inhibitors; RNA: ribonucleic acid; SCr: serum creatinine; TDF: tenofovir disoproxil fumarate; TMP-SMX: trimethoprim-sulphamethoxazole

§Definitions used: Renal impairment: $\geq 25\%$ decreased in eGFR from baseline or development of CKD; Mild renal impairment: eGFR 60-89 mL/min/1.73m²; Chronic kidney disease: eGFR 15-59mL/min/1.73m²; Anaemia: Haemoglobin in male<130g/L; Haemoglobin in female<120g/L

Table 2. Factors Associated with Tenofovir- Induced Renal Impairment

Variables	Univariable Logistic Regression (n=314)	
	Crude Odds Ratio (95% CI)	p-value
Age, per 5 year increment	1.50 (1.24-1.80)	<0.001
Anaemia	2.41 (1.11-5.21)	0.026
Hypertension	6.10 (2.66-14.0)	<0.001
Baseline eGFR, per 10mL/min increase	1.14 (0.98-1.32)	0.101
Body weight, per 5kg decrement	1.23 (1.02-1.47)	0.029
ART experience	2.91 (1.25-6.75)	0.013
Baseline SCr, per 5 μ mol/L decrement	1.09 (0.96-1.22)	0.219
Mild renal impairment	1.82 (0.847-3.92)	0.125
History of AKI	3.99 (0.94-4.35)	0.108
Previous history of AIDS-defining illness	2.27 (0.94-5.46)	0.068
Nadir CD4 cells counts, per 10 cells cells/ μ L	1.03 (1.00-1.07)	0.063
Concurrent nephrotoxic drug	2.02 (0.94-4.35)	0.072
Female	2.38 (0.89-6.33)	0.082
History of anaemia before TDF initiation	1.77 (0.83-3.76)	0.141
Concurrent ritonavir-boosted PI used	1.58 (0.56-4.40)	0.387
Baseline CD4 <200 cells/ μ L	1.46 (0.69-3.11)	0.321
Baseline HIV RNA, per log10/mL	0.92 (0.74-1.13)	0.426
Hepatitis C co-infection	2.41 (0.26-22.3)	0.437

Diabetes mellitus	1.83 (0.59-5.72)	0.297
Liver Impairment	0.80 (0.18-3.59)	0.776
Dyslipidaemia	1.55 (0.66-3.64)	0.319
Alcohol consumption	1.13 (0.47-2.72)	0.788
Smoking	0.76 (0.30-1.93)	0.569
Duration of TDF	0.99 (0.96-1.02)	0.418

Model 1 (all patients)	Multivariable Logistic Regression* (n=314)	
	Adjusted Odds Ratio (95% CI)	p-value
Age, per 5 year increment	1.46 (1.16-1.76)	0.001
Anaemia	2.62 (1.12-6.13)	0.027
Hypertension	3.49 (1.28-9.46)	0.014
Baseline eGFR, per 10mL/min increase	1.22 (1.10-1.48)	0.007
Model 2 (excluding patients with a history of AKI, mild renal impairment and exposure to nephrotoxic drugs)	Multivariable Logistic Regression† (n=171)	
	Adjusted Odds Ratio (95% CI)	p-value
Age, per 5 year increment	1.47 (1.16-1.76)	0.001
Hypertension	3.18 (1.20-8.48)	0.020
Baseline eGFR, per 10mL/min increase	1.21 (1.10-1.48)	0.007

*Forward Selection and Backward Elimination LR Multiple Logistic Regression model was applied for the main model (Model 1). Linearity of continuous variables were assessed and found to be linear in the model. Multi-collinearity and interaction between independent variables were checked and not found. Assumptions of models fitness were identified by performing Pearson Chi-square test (p=0.8726), Hosmer-Lemeshow test (p=0.2350), classification table (overall correctly classified percentage = 91.72%) and area under the ROC curve (80.13%).

†Abbreviations: AIDS: acquired immune-deficiency syndrome; AKI: acute kidney injury; ART: anti-retroviral therapy; CI: Confidence Interval; eGFR: estimated glomerulus filtration rate; HIV: human immune-deficiency virus; PI: protease inhibitors; RNA: ribonucleic acid; SCr: serum creatinine; TDF: tenofovir disoproxil fumarate

Figure 1. Patient disposition

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Patients included in final analysis
 n=314

344 ART: anti-retroviral therapy; eGFR: estimated glomerulus filtration rate; SCr: serum
 345 creatinine; TDF: tenofovir disoproxil fumarate; UMMC: University Malaya Medical Centre

346 **Figure 2. Trajectory of eGFR following TDF initiation in individuals (A) with and**
 347 **without renal impairment; and (B) treatment-experienced vs treatment-naïve.**

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References

- WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. In: WHO, editor. Geneva: WHO; 2013. p. 96-111.
- Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med.* 2005; 6(4): 284-90.
- Gallant JE, Winston JA, DeJesus E, Pozniak AL, Chen SS, Cheng AK, et al. The 3-year renal safety of a tenofovir disoproxil fumarate vs. a thymidine analogue-containing regimen in antiretroviral-naïve patients. *AIDS.* 2008; 22(16): 2155-63.
- Cassetti I, Madruga JV, Suleiman JM, Etzel A, Zhong L, Cheng AK, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. *HIV Clin Trials.* 2007; 8(3): 164-72.

5. Chaisiri K, Bowonwatanuwong C, Kasettrat N, Kiertiburanakul S. Incidence and risk factors for tenofovir-associated renal function decline among Thai HIV-infected patients with low-body weight. *Curr HIV Res.* 2010; 8(7): 504-9.
6. 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. *Clin Infect Dis.* 2005; 40(8): 1194-8.
7. Madeddu G, Bonfanti P, De Socio GV, Carradori S, Grosso C, Marconi P, et al. Tenofovir renal safety in HIV-infected patients: results from the SCOLTA Project. *Biomed Pharmacother.* 2008; 62(1): 6-11.
8. Nishijima T, Komatsu H, Gatanaga H, Aoki T, Watanabe K, Kinai E, et al. Impact of small body weight on tenofovir-associated renal dysfunction in HIV-infected patients: a retrospective cohort study of Japanese patients. *PLoS One.* 2011; 6(7): e22661.
9. Peyriere H, Reynes J, Rouanet I, Daniel N, de Boever CM, Mauboussin JM, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J Acquir Immune Defic Syndr.* 2004; 35(3): 269-73.
10. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis.* 2013; 207(9): 1359-69.
11. Pujari SN, Smith C, Makane A, Youle M, Johnson M, Bele V, et al. Higher risk of renal impairment associated with tenofovir use amongst people living with HIV in India: a comparative cohort analysis between Western India and United Kingdom. *BMC Infect Dis.* 2014; 14: 173.
12. Laprise C, Baril JG, Dufresne S, Trottier H. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. *Clin Infect Dis.* 2013; 56(4): 567-75.
13. Calza L, Trapani F, Tedeschi S, Piergentili B, Manfredi R, Colangeli V, et al. Tenofovir-induced renal toxicity in 324 HIV-infected, antiretroviral-naïve patients. *Scand J Infect Dis.* 2011; 43(8): 656-60.
14. Bickel M, Khaykin P, Stephan C, Schmidt K, Buettner M, Amann K, et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration. *HIV Med.* 2013:633-8.
15. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS.* 2009; 23(15): 1971-5.

16. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Ann Intern Med.* 2003; 139(2): 137-47.
17. Levey AS, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol.* 2000; 11: 155A.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999; 130(6): 461-70.
19. Cao Y, Han Y, Xie J, Cui Q, Zhang L, Li Y, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. *BMC Infect Dis.* 2013; 13: 301.
20. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS.* 2007; 21(10): 1273-81.
21. Brennan A, Evans D, Maskew M, Naicker S, Ive P, Sanne I, et al. Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir. *AIDS.* 2011; 25(13): 1603-9.
22. Kamkuemah M, Kaplan R, Bekker L-G, Little F, Myer L. Renal impairment in HIV-infected patients initiating tenofovir-containing antiretroviral therapy regimens in a Primary Healthcare Setting in South Africa. *Tropical Medicine & International Health.* 2015; 20(4): 518-26.
23. 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.* 2014; 28(13): 1903-10.
24. Baxi SM, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, et al. Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women. *AIDS.* 2014; 28(1): 59-66.
25. Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis.* 2008; 197(1): 102-8.

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Figure 2. Trajectory of eGFR following TDF initiation in individuals (A) with and without renal impairment; and (B) treatment-experienced vs treatment-naïve.

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