Tenofovir disoproxil fumarate associated nephrotoxicity: a retrospective cohort study at two referral hospitals in Namibia.

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Abstract

Introduction: The incidence and risk factors of tenofovir (TDF)-related renal impairment (RI) in Namibia are unknown where TDF-containing ART regimens are used as the first line for HIV. Methodology: A retrospective cohort study among HIV infected patients at two intermediate hospitals. A decline in estimated glomerular filtration rate (eGFR) was significant if it was ≥25% and included a change to a lower eGFR stage. New-onset RI was defined as an eGFR <50 ml/min/1.73m². Results: 10 387 patients were included: 11.4% (n=1,182) experienced the decline in eGFR. Of these, 0.6% (n=62) migrated to eGFR stages IV and V. The incidence was 4.5 (95%CI: 4.3 – 4.8) per 100 patient years. RI developed in 400 patients for an incidence rate of 2.4 (95%CI: 2.2 – 2.6) cases per 100 patient years. Risk factors with effect sizes >2.0, for decline-in-eGFR were baseline eGFR >60 (aHR=15.6); hyperfiltration (aHR=5.0); and pregnancy (aHR=2.4); while for RI they were hyperfiltration (aHR=4.1) and pregnancy (aHR=29). Conclusion: The incidence of decline-in-eGFR was higher than in other sub-SSA countries, but not RI. A high baseline eGFR had the greatest risk for the decline, and hyperfiltration for the RI.

Introduction

In the pre-antiretroviral therapy (ART) era, the incidence of human immunodeficiency virus (HIV) associated renal disease was high,[1,2] but was subsequently appreciably reduced by ART. Presently, tenofovir disoproxil fumarate (TDF)-containing ART regimens are associated with clinically significant decline in renal function.[1–7] TDF– associated renal toxicity occurs at the proximal tubules. [8,9] Tenofovir accesses proximal tubular cells via organic anion transporters (OATs),[10] where it inhibits mitochondrial DNA polymerase gamma resulting in clinically significant reductions renal function [8,11–14]. The incidence of TDF-associated decline in estimated glomerular filtration rate (eGFR) has been estimated at 1.8 to 16.2 per 100 patient years [6,15–18]. The decline in eGFR could culminate in end stage renal disease impacting public health resources [19], thus is particularly important in a country with a high prevalence of both cardiovascular diseases alongside HIV but with high rates of virally suppressed HIV[1,3]. There is varying evidence regarding the factors for TDF-associated decline in renal function, including a high baseline eGFR,[2,6,7,16,20–27] duration of exposure to TDF-containing ART;[6,17,28–33] gender;[29,34–36] and pregnancy.[26,37]

Given the varying information concerning the risk factors for TDF-associated renal toxicity, coupled with the lack of knowledge regarding its incidence in Namibia, the primary objective of this study was to estimate the incidence of clinically significant decline in eGFR and identify the risk factors associated with this decline. The secondary objective was to estimate the incidence rate of new-onset renal impairment. We hypothesised that the incidence rate of decline in eGFR was 2.0 cases per 100 patient years based on the findings from other sub-Saharan African (SSA) countries by Salome et al and Mulenga et al., [25,32] The incidence rate of new-onset renal impairment (RI) was hypothesised at

3.0 cases per 100 patient years, based on findings by Quesada *et al* [6] The findings from the present study can guide the future management of patients with HIV in Namibia and other SSA countries where TDF-containing ART regimens are used as first-line treatment.

Methodology

Study design and setting

This was a retrospective cohort study of HIV infected patients who received HIV care and treatment at Oshakati Intermediate Hospital (Northern Namibia) and Katutura Intermediate Hospital (Central), both of which are public referral hospitals in Namibia. Together, these facilities have a bed occupancy of 1,580, are ~750km apart, and provided ART to about 40,000 HIV positive patients in 2016.

Inclusion/ exclusion criteria

Patients were included in the cohort if they had initiated ART from 01 August 2010 through December 2016; were 16 years and older at initiation of ART; and had received a TDF-containing ART regimen. (NB: Renal function tests were only conducted for patients who were receiving TDF-containing ART, and in Namibia, TDF-containing first-line ART regimens became preferred over zidovudine-based regimens in July 2010 [38]. These guidelines recommended renal function assessments at baseline, 3 months, 6 months, then every 6 months[39]. Patients were excluded for lacking gender or duration of follow-up.)

Source of Data

The data was acquired from the central electronic Patient Management System (ePMS) hosted by the Monitoring and Evaluation (M&E) unit of the Ministry of Health and Social Services (MoHSS). Data are routinely entered into health facility ePMS databases from patient treatment files by data clerks. The data is regularly sent electronically to the M&E unit. These data include patient demographics, clinical and medical records. Based on the serum creatinine (SeCr) from the clinical data we calculated the eGFR using the CKD-EPI (Chronic Kidney Disease Epidemiology) formula:

$$eGFR = 141 * \min(Scr/\kappa, 1)_\alpha * \max(Scr/\kappa, 1) – 1.209 * 0.993_{Age} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}$$

Therefore, there were five eGFR stages with the following eGFR limits: stage I, $\geq$90 ml/min/1.73m^2; stage II, 60-89 ml/min/1.73m^2; stage III, 30-59 ml/min/1.73m^2; stage IV, 15-29 ml/min/1.73m^2; and stage V, <15 ml/min/1.73m^2.

Outcomes and endpoints

Decline in eGFR

We investigated the rate of decline in eGFR. The criteria we used to assign 'decline in eGFR' status to a patient were: (1) a >25% drop in eGFR or (2) a 1.5x increase in serum creatinine (SeCr) and (3) a transition to a lower eGFR stage. We adapted the first and second criteria from the RIFLE criteria, which identifies renal pathology starting with a >25% drop in eGFR or a $\geq$1.5 increase in SeCr[40]. When a patient's follow-up eGFR or SeCr met criterion one or two, we subjected it to criterion three, which when met we assigned the 'decline in eGFR' status to the patient. Therefore, there were two outcome groups: decline and non-decline. Patients in the decline group who had only two eGFR records – baseline and last – the endpoint was, by default, the day the last eGFR was recorded. For patients who had more than two eGFR records, we reviewed the previous eGFR(s) to identify the day the first decline occurred, and this day served as the end of the follow-up period, where applicable. For patients in the non-decline group, the end of the follow-up period was, by default, the day the last eGFR was recorded.

New-onset renal impairment

We investigated the new-onset renal impairment amongst patients who had a baseline eGFR $\geq$60 ml/min/1.73m^2. Renal impairment was defined as an eGFR <50 ml/min/1.73m^2, as it is at this eGFR

level that dosage interventions are implemented. The patient was assigned the 'new-onset renal impairment' status based on the last eGFR. The day the last eGFR was recorded served as the end of follow-up.

Transition to lower eGFR stages

We investigated the rate of transition to lower eGFR stages with or without the >25% drop in eGFR. We depended on the stage of the last eGFR for this investigation.

Independent variables

The independent continuous variables were age, body weight, and follow-up duration. The categorical variables were gender, pregnancy, hepatitis B co-infection, isoniazid preventive therapy (IPT), hyperfiltration, tuberculosis, and the stage of eGFR at baseline, CD4 count category (<200 cells/mm^3 and a count $\geq$200 cells/mm^3) and viral load category (<1000 copies/L and $\geq$1000 copies/L). NB: Basing on the articles by Cachat *et al*., and Tonneijck *et al*., we defined hyperfiltration as an eGFR $\geq$135 ml/min/1.73m^2. [41–43] We assigned diabetes- and hypertension- related states (diabetes mellitus/ pre-diabetes, or hypertension/ pre-hypertension) to patients who had hyperfiltration at baseline, since it is a marker of renal impairment in patients with these disease states. [44–47]

Data analysis

The means and standard deviations (SD) of the baseline continuous variables, and proportions of patients for categorical variables, were used to describe the characteristics of the cohort. These parameters were calculated, at follow-up, for the decline and non-decline groups. We conducted Pearson and Spearman correlation analyses to understand how the variables related with each other. We estimated the incidence rate of decline in eGFR for the whole cohort, then for each baseline stage, using the OpenEpi® calculator. We estimated the incidence rate of new-onset RI. We estimated the incidence rate of transitioning to lower eGFR stages from the baseline stage. We compared the incidence rates for patients who were in eGFR stage I, the reference group, with the incidence rates for patients who were in stages II, III, and IV.

We identified patients who met the criteria for decline in eGFR and divided the cohort into decline and non-decline groups. We compared the decline and non-decline groups for any differences in the independent variables using the Student's *t* and Pearson's chi-square tests, for continuous and categorical variables, respectively. To identify the predictors of decline in eGFR, we used cox-regression analysis. First, we conducted univariate analysis for each independent variable, then multivariate analysis to adjust for the effects of covariates. We applied the backward conditional method. Because of varying endpoints, we conducted analysis using binary logistic regression to see if the findings were like the cox-regression findings. We run the first analysis without the duration of follow-up variable and included it for the second. In addition, we conducted gender specific binary logistic regression sub-analyses, purposely to evaluate the effect of some variables that were biased by gender such as the pregnancy experience, and to find out if the significant differences between males and females had significant effects when single gender analyses were conducted.[48] We identified patients who experienced new-onset RI and divided the sub-cohort into two groups: the group that experienced new-onset RI and the group that did not. To identify predictors of new-onset RI, we conducted cox-regression analysis. First, we conducted univariate analysis for each independent variable, followed by a multivariate analysis using the backward conditional method. Like above, because of widely varying endpoints, we conducted binary logistic regression analysis for similarity of findings with the cox-regression findings. We run the analysis without and then with the duration of follow-up variable. For all analyses, the confidence intervals were set at 95%, and significance at <0.05. SPSS version 22 was employed.

Ethics

Patient confidentiality was assured by the elimination of identifier variables. The data was secured on a password protected computer and was available to the data analyst only. This study was approved by the ethics review board of the University of Namibia and the Ministry of Health and Social Services. The reference of the approval letter is Ref 17/3/3.

Findings

Baseline characteristics

A total of 10,387 patients were included in the study (Figure 1). On average each patient received 2.4 renal function tests. Most were female (67.5%). The baseline means and standard deviations (SD) for continuous variables are documented in table 1. Proportions for the categorical variables are documented in table 1. Males were significantly older and had a higher baseline eGFR. A notable proportion of patients (35.1%) had a baseline eGFR <60 ml/min/1.73m^2, with a significantly lower proportion of male. Few patients, the majority of which were male, had hyperfiltration at baseline. During follow-up, 99.2% were receiving TDF-containing ART, of which 5.9% were on second-line ART, with more males than females. There were significantly more males than females with a CD4 count <200 and a VL ≥1000 copies/L Pregnancy occurred in 2.8% of the females. (Table 1).

Decline in eGFR: Incidence rates and differences between decline and non-decline groups

Of the 10,387 patients, 11.4% (n=1182) experienced a decline in eGFR. The decline group had a higher mean baseline eGFR; higher proportion of patients in eGFR stages I and II; a lower mean age; a higher proportion of patients with hyperfiltration at baseline; and a higher proportion of pregnancy occurrences (Table 2). The incidence rate of decline in eGFR was 4.5 cases per 100 patient years. The incidence rate of decline in eGFR amongst patients in eGFR in stage I was 2.0, 11.1, and 12.5 times that for patients in eGFR stages II, III, and IV, respectively (Table 3).

Figure 1: Selection of patients included in the study from OIH and KIH, Namibia

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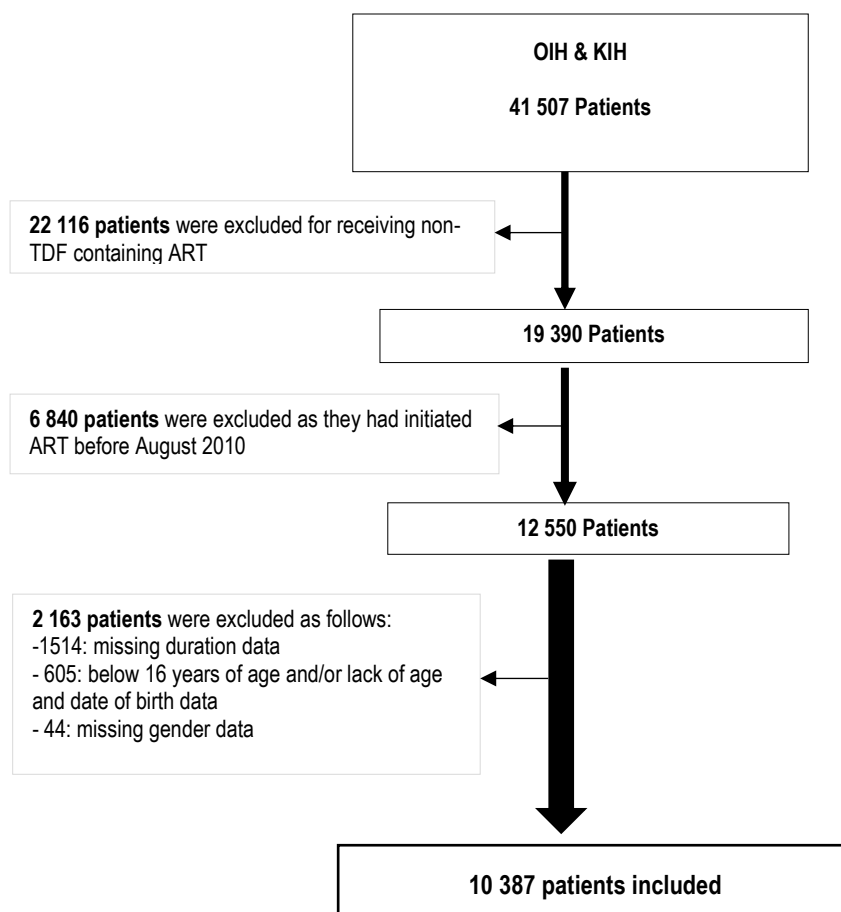
Description, figure 1: The figure provides the process by which exclusion and inclusion criteria were applied, eventually selecting 10, 387 patients were selected for inclusion in the study

New-onset RI: Incidence rates and differences between new-onset RI and non-new-onset RI groups

Of the 6,744 patients in eGFR stages I and II at baseline, 5.9% (n=400) experienced new-onset RI, some of whom (0.7% [n=44]) transitioned to severely reduced eGFR stages IV and V. RI was experienced by significantly higher proportions of females; eGFR stage II patients; patients with a CD4 count >200; and patients who experienced pregnancy. (Table 2). The incidence rate of new-onset renal impairment was 2.4 cases per 100 patient years. For patients who were in eGFR stage I at baseline, the incidence rate of new-onset RI was significantly lower than eGFR stage II patients (1.0 vs. 3.2 per 100 patient years; rate ratio = 3.0, $p<0.001$). Notably, the incidence rate of transition to eGFR stages IV and V combined, was not significantly different between patients in eGFR stages I and II (1.8 vs. 3.1 per 1000 patient years; rate ratio = 0.7, $p=0.516$), but was significantly lower than that for patients in eGFR stage III (1.8 vs. 10.0 per 1000 patient years; rate ratio = 0.2, $p<0.001$) (Table 3).

Table 1: Summary of patient characteristics, with gender distributions

	Variables	All (N=10 387)	Female (n=7020)	Male (n=3367)	p-value
Baseline					
*e*GFR Stage, n (%) baseline	Stage I: ≥90	2496 (24.0)	1288 (18.4)	1208 (35.9)	
	Stage II: 60 - 89	4248 (40.9)	2788 (39.7)	1460 (43.4)	
	Stage III: 30 - 59	3383 (32.6)	2719 (38.7)	664 (19.7)	<0.001
	Stage IV: 15 - 29	216 (2.1)	196 (2.8)	20 (0.6)	
	Stage V: <15	44 (0.4)	29 (0.4)	15 (0.4)	
Mean (SD)	eGFR, baseline	72 (28)	68 (25)	82 (29)	<0.001
	Age, baseline	39 (9)	37 (9)	42 (9)	<0.001
	Weight (kg), baseline	63 (14)	63 (14)	63 (14)	0.50
	Duration of follow-up	2.5 (1.7)	2.5 (1.7)	2.5 (1.7)	0.951
n (%) of patients	Hep-B surface antigen positive	55 (0.5)	27 (0.4)	28 (0.8)	0.003
Follow-up variables					
n (%) patients who received/ had	TDF regimens with a PI	608 (5.9)	376 (5.4)	232 (6.9)	0.002
	IPT	1371 (13.2)	956 (13.6)	415 (12.3)	0.068
	TB therapy	320 (3.1)	185 (2.6)	135 (4.0)	<0.001
	CD4 count <200	1497 (14.4)	897 (12.8)	600 (17.8)	<0.001
	Viral load ≥ 1000	2235 (21.5)	1385 (19.7)	850 (25.2)	<0.001
	Pregnancy	198 (1.9)	198 (2.8)	n/a	n/a
	Hyper-filtration (Pre-diabetes and Pre-hypertension)	110 (1.1)	39 (0.6)	73 (2.2)	<0.001

Data explained:

Low mean duration of follow-up: The cohort studied includes patients who initiated ART in the period stretching from August 01, 2010 to December 2016. As such, some patients were only followed-up for short periods. Some patients who initiated ART in as early as August 2010, were lost to follow-up. Also, loss to

follow-up applied to patients who initiated ART at any time during the period studied. These two factors contributed to the low duration of follow-up.

The TDF regimen with a PI: This included the following regimens: TDF/ 3TC or FTC/ AZT or no ARV and LPV/r , ATV/r, IDV/r, and SQV/r. Other patients were receiving first-line ART which consisted of TDF/3TC or FTC/ and EFV or NVP. Abbreviations: 3TC=Lamivudine, FTC=Emtricitabine, AZT=Zidovudine, ARV=Antiretroviral, LPV/r=Lopinavir/ritonavir, ATV/r=Atazanavir/ritonavir, EFV=Efavirenz and NVP=Nevirapine.

Correlation analysis results

Heavier patients were more likely to have a lower baseline eGFR (r^2 = **-0.6**, *p<0.001*); a lower follow-up eGFR (r^2 = **-0.6**, *p<0.001*); and were less likely to have hyperfiltration. Male gender was correlated with a higher baseline (r^2 = 0.3, *p<0.001*) and follow-up eGFR (r^2 = 0.3, *p<0.001*). A higher baseline eGFR was positively correlated with decline in eGFR (r^2 = 0.3, *p<0.001*), but also with a higher baseline eGFR was associated with a higher follow-up eGFR (r^2 = **0.6**, *p<0.001*). Other correlations are available in the supplementary document.

Table 2: Comparisons between the decline and non-decline groups

Variables		N=10 387[1]			N=6744[2]		
		Non-Decline (n=9 205)	Decline (n=1 182)	*p*-value	No RI	New onset RI	*p*-value
Gender	Female	6246 (67.9)	774 (65.5)	0.101	3794 (59.8)	282 (70.5)	**<0.001**
	Male	2595 (32.1)	408 (34.5)		2550 (40.2)	118 (29.5)	
eGFR stages, n (%) baseline	Stage I: ≥90	1885 (20.5)	611 (51.7)		2431 (38.3)	65 (16.3)	
	Stage II: 60 - 89	3758 (40.8)	490 (41.5)		3913 (61.7)	335 (83.8)	
	Stage III: 30 - 59	3307 (35.9)	76 (6.4)	**<0.001**	-	-	**<0.001**
	Stage IV: 15 - 29	211 (2.3)	5 (0.4)		-	-	
	Stage V: <15	44 (0.5)	-		-	-	
eGFR stages, n (%) follow-up	Stage I: ≥90	2211 (24.0)	-		2093 (33.0)	-	
	Stage II: 60 - 89	4028 (43.8)	453 (38.4)		3515 (55.4)	-	
	Stage III: 30 - 59	2901 (31.5)	603 (51.0)	**<0.001**	736 (11.6)	356 (89.0)	-
	Stage IV: 15 - 29	60 (0.7)	99 (8.4)		-	36 (9.0)	
	Stage V: <15	5 (0.1)	26 (2.2)		-	8 (2.0)	
Mean (SD)	Baseline eGFR	70 (25)	94 (34)	**<0.001**	87.2 (23.1)	77.1 (21.0)	**<0.001**
	Follow-up eGFR	73 (23)	55 (18)	**<0.001**	82.3 (19.6)	40.6 (8.9)	**<0.001**
	Baseline age	39 (9)	38 (9)	**0.002**	39.5 (9.5)	37.0 (9.0)	0.277
	Baseline weight (kg)	64 (14)	63 (13)	0.445	57.7 (9.6)	68.3 (12.2)	**<0.001**
	Duration of follow-up	2.6 (1.6)	2.1 (1.7)	**<0.001**	2.5 (1.7)	2.2 (1.7)	0.945
No and percentage of patients who received/ had	TDF regimens with a PI	543 (5.9)	65 (1.5)	0.581	370 (5.9)	23 (5.9)	0.946
	IPT	1222 (13.3)	149 (12.6)	0.522	839 (13.2)	47 (11.8)	0.397
	TB therapy	290 (3.2)	30 (2.5)	0.251	226 (3.6)	10 (2.5)	0.262
	Hep-B surface antigen +ve	49 (0.5)	6 (0.5)	0.912	40 (0.6)	1 (0.3)	0.342
	CD4 count <200	1347 (14.6)	150 (12.7)	0.073	1005 (15.8)	48 (12.0)	**0.040**
	Viral load ≥ 1000	1993 (21.7)	242 (20.5)	0.345	1423 (22.4)	90 (22.5)	0.974
	Pregnancy	163 (1.8)	35 (3.0)	**0.005**	91 (1.4)	15 (3.8)	**<0.001**
	Hyper-filtration	47 (0.5)	65 (5.5)	**<0.001**	201 (3.2)	17 (4.3)	0.235

[1]The full cohort of patients who were assessed for decline in eGFR. The difference between the decline and non-decline groups were assessed for all the independent variables. [2]These are the patients who were in eGFR stages I and II at baseline. This group of patients were assessed for new-onset RI. Differences between the patients who experienced the and those who did not experience RI were evaluated. For both groups, were significant differences were observed, the *p*-value is boldened.

Table 3: Incidence rates of decline in eGFR, RI and transition to lower baseline eGFR stages, and a comparisons

Stage of eGFR at baseline	Patient years	Cases (%)	Incidence rate (95%CI)					Incidence rate comparisons (95% CI)					P-value
			>25% decline and transition to lower eGFR stages	New-onset eGFR needing dosage adjustment	New eGFR stage III	New eGFR stage IV	New eGFR Stage V	>25% decline and transition to lower eGFR stages	New-onset eGFR needing dosage adjustment	New eGFR stage III	New eGFR stage IV	New eGFR Stage V	
All	26,029.4	1182 (11.4)[1]	4.5 (4.3 – 4.8)	-	-	-	-	-	-	-	-	-	-
I & II	16,808	400 (6.2)[2]	-	2.4 (2.2 – 2.6)	-	-	-	-	-	-	-	-	-
I & II	16,808	1088 (16.1)[3]	-	-	6.5 (6.1 – 6.9)	-	-	-	-	-	-	-	-
I to III	25,310.3	108 (10.7)[4]	-	-	-	4.3 (3.5 – 5.1)[a]	-	-	-	-	-	-	-
I to IV	25,923.1	27 (0.3)[5]	-	-	-	-	1.0 (0.7 – 1.5)[a]	-	-	-	-	-	-
I	6182	611 (24.5)[1]	9.9 (9.1 – 10.7)	-	-	-	-	Reference	-	-	-	-	-
		65 (2.6)[2]	-	1.1 (0.8 – 1.3)	-	-	-	-	Reference	-	-	-	-
		146 (5.9)[3]	-	-	2.4 (2.0 – 2.8)	-	-	-	-	Reference	-	-	-
		7 (0.3)[4]	-	-	-	3.0 (2.0 – 6.0)[a]	-	-	-	-	Reference	-	-
		4 (0.2)[5]	-	-	-	-	6.4 (2.1 – 15.6)[b]	-	-	-	-	Reference	-
II	10,626	490 (41.5)[1]	4.6 (4.2 – 5.0)	-	-	-	-	0.5 (0.4 – 0.5)	-	-	-	-	<0.001
		335 (8.4)[2]	-	3.2 (2.8 – 3.5)	-	-	-	-	3.0 (2.3 – 4.9)	-	-	-	<0.001
		942 (22.2)[3]	-	-	8.9 (8.3 – 9.5)	-	-	-	-	3.2 (3.8 – 4.5)	-	-	<0.001
		29 (0.7)[4]	-	-	-	2.7 (1.9 – 3.9)[a]	-	-	-	-	2.4 (1.1 – 5.5)	-	0.031
		4 (0.09)[5]	-	-	-	-	3.8 (1.2 – 9.1)[b]	-	-	-	-	0.6 (0.2 – 2.3)	0.219
III	8502.3	76 (2.3)[1]	2.3 (1.8 – 2.8)	-	-	-	-	0.09 (0.07 – 0.12)	-	-	-	-	<0.001
		72 (2.1)[4]	-	-	-	2.1 (1.7 – 2.7)	-	-	-	-	0.4 (0.3 – 0.5)	-	0.371
		13 (0.3)[5]	-	-	-	-	3.8 (2.1 – 6.4)[a]	-	-	-	-	2.4 (0.8 – 8.4)[b]	0.121
IV	612.8	6 (0.4)[1]	8.2 (3.0 – 18)[a]	-	-	-	-	0.08 (0.03 – 0.2)	-	-	-	-	<0.001
V	106.2	-	-	-	-	-	-	-	-	-	-	-	-

[1]Cases of decline; [2]Cases with RI; [3]Cases with new stage III eGFR; [4]Cases of new stage-IV eGFR; [5]Cases of new stage-V eGFR; [a] Per 1000 and [b] Per 10 000 patient-time years. At the beginning of ART, 2005 (19.3%) needed dosage adjustments. Of these, during the follow-up period, 847 (42.2% of the 2005) transitioned to eGFRs requiring normal doses. Of the 8382 who needed normal TDF doses 776 (9.3%) transitioned to the need for dosage adjustment, 448 (5.3%) of whom originally had eGFRs in stages I and II. normalisation of adjustment. Ultimately, those who needed dosage adjustment were 1934 (18.6%). Of the eGFR stage I patients, 611 experienced decline in eGFR, of which 65 (10.6%) needed dose adjustment. For the 490 in eGFR stage II patients, 490 experienced decline in eGFR, of which 299 (61.0%) needed dose adjustment

Risk factors for decline in eGFR and new-onset renal impairment

Patients with a baseline eGFR ≥60 ml/min/1.73m2 (stages I and II) were at a greater risk of experiencing decline in eGFR (aHR=15.6), (Figure 2). The same applied to patients who had hyperfiltration (aHR=5.0), and those who experienced pregnancy during follow-up (aHR=2.5). The probability of experiencing a decline in eGFR was 30% higher in females (aHR=1.3). Every unit rise in body weight was associated with a 3.9% probability of experiencing a decline in eGFR (aHR=1.039), (Table 4). Regarding RI, there was a four times risk of experiencing new-onset RI for patients who had hyperfiltration at baseline (aHR=4.0). The risk of new-onset RI amongst patients who experienced pregnancy during follow-up was ~3.0times that of those who did not experience pregnancy (aHR=2.9), and the risk amongst females was ~2.0times that in males (aHR=1.9). Patients in eGFR stage II, were 70% more likely to experience new-onset RI than patients in the eGFR stage I category (aHR=1.7). Each unit rise in body weight was associated with an 8.0% increase in the probability of experiencing RI (aHR=1.08), (Table 5).

Table 4: Predictors of decline in eGFR

Variable	Univariate analysis			Multivariate		
	Crude HR	95% CI	p-value	Adjusted HR	95% CI	*p*-value
eGFR baseline >60	7.5	(6.0 – 9.4)	**<0.001**	15.6	(12.1 – 20.1)	**<0.001**
Hyperfiltration	3.6	(2.9 – 4.4)	**<0.001**	5.0	(4.1 – 6.1)	**<0.001**
Pregnancy	2.5	(1.8 – 3.5)	**<0.001**	2.4	(1.7 – 3.5)	**<0.001**
Female gender	0.9	(0.8– 1.02)	0.081	1.3	(1.1 – 1.5)	**<0.001**
Weight	1.0	(1.0 – 1.0)	0.585	1.039	(1.035 – 1.044)	**<0.001**
Age	0.983	(0.977 – 0.990)	**<0.001**	0.976	(0.969 – 0.983)	**<0.001**
Second-line ART	0.7	(0.5 – 0.9)	0.002	0.7	(0.5 – 0.9)	**<0.001**
CD4 count >200	1.0	(0.8 – 1.1)	0.657	-	-	-
TB event	1.0	(0.7 – 1.4)	0.770	-	-	-
Viral Load >1000	1.0	(0.8 – 1.1)	0.681	-	-	-
Isoniazid Preventive Therapy	1.0	(0.9 – 1.2)	0.928	-	-	-
Hepatitis-B	1.1	(0.5 – 2.4)	0.831	-	-	-

Results of univariate and multivariate analysis using cox-regression analysis for the investigation of predictors of decline in eGFR. The p-values for predictors are boldened. Multivariate analysis made female gender and higher baseline weights predictors.

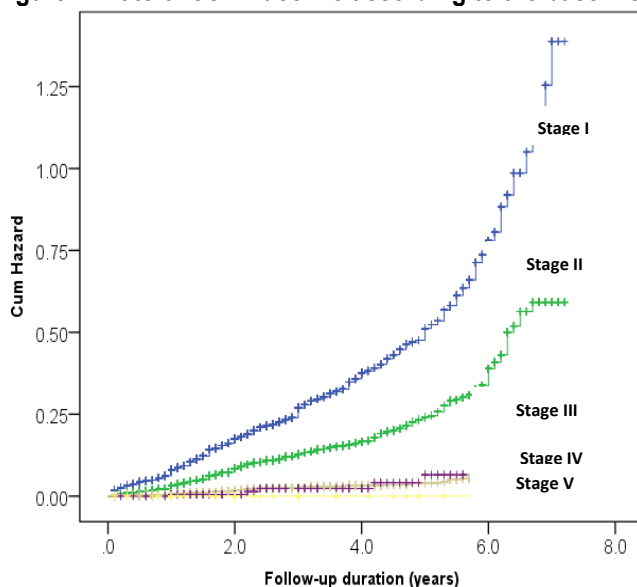**Figure 2: Rate of eGFR decline according to the baseline stage**

Figure 2: The cumulative trend of events of decline in eGFR, showing faster trends in stage I followed by stage II patients, with minimal changes in stages III and V.

Table 5: Factors associated with RI (n=6744)

Variable	Univariate analysis			Multivariate analysis		
	Crude HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Hyperfiltration	1.4	(0.9 – 2.3)	0.145	4.1	(2.3 – 7.1)	<0.001
Pregnancy	3.7	(2.2 – 6.2)	<0.001	2.9	(1.7 – 4.8)	<0.001
Female gender	1.6	(1.3 – 2.0)	<0.001	1.9	(1.5 – 2.4)	<0.001
Baseline GFR stage II	3.0	(2.3 – 3.9)	<0.001	1.7	(1.2 – 2.3)	0.001
Weight	1.076	(1.069 – 1.083)	<0.001	1.08	(1.07 – 1.09)	<0.001
Age	0.965	(0.955 – 0.976)	<0.001	0.97	(0.96 – 0.98)	<0.001
Second-line ART	0.7	(0.5 – 1.1)	0.093	-	-	-
CD4 count >200	1.1	(0.8 – 1.5)	0.529	-	-	-
TB event	0.8	(0.4 – 1.5)	0.546	-	-	-
Viral Load >1000	1.0	(0.8 – 1.3)	0.890	-	-	-
Isoniazid Preventive Therapy	0.9	(0.7 – 1.3)	0.608	-	-	-
Hepatitis-B	0.5	(0.1 – 3.3)	0.445	-	-	-

Results of univariate and multivariate analysis using cox-regression analysis for the investigation of predictors of RI. The p-values for predictors are boldened. Multivariate analysis made hyperfiltration a predictor.

Figure 3: Transition to severe- and end-stage-renal disease stages for patients with baseline stages I to II
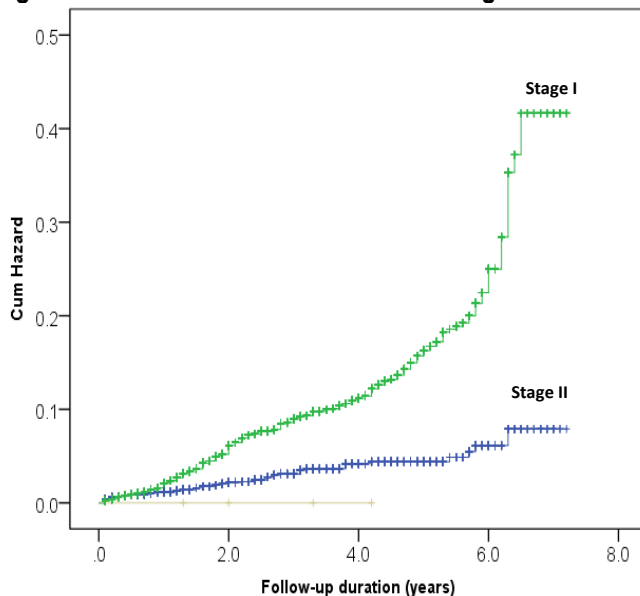

Figure 3 showing higher proportions of patients transitioning from eGFR stage I than II to eGFR stages IV and V.

Discussion

This is the first relatively large study on the incidence and risk factors for TDF-associated renal adverse outcomes in Namibia. Overall, the incidence rate of decline in eGFR was relatively higher than what we observed in other SSA countries. The risk factors included a high baseline eGFR, hyperfiltration, pregnancy, female gender, and higher body weight. The incidence rate of new-onset RI was relatively like what we observed in other studies. The risk factors RI were like the ones for decline in eGFR, except that a high baseline eGFR (stage I) was not a risk factor RI. However, it should be noted that decline in eGFR was not always clinically significant, but RI was. The incidence rate of transition to lower eGFR stages was higher in the lower renal function stages, making our findings consistent with the fact that TDF should be used in patients with low baseline CD4 counts, with caution. Nevertheless, a significant proportion of patients had a low baseline eGFR at baseline, received TDF, and the rate of decline in eGFR was low.

The proportion of patients with a low baseline eGFR in sub-Sahara African countries, varied greatly. For example, Mulenga *et al.,* found that 1.9% and 4.0% of the patients in the TDF and non-TDF groups were in moderate and severe reduced eGFR at baseline,[25] while the proportions of patients with moderate and/or severe eGFR at baseline by Kamkuemah *et al.,* Assaram *et al.,* Bonaventura *et al.,* and Msango *et al.,* respectively were, 2%, 9.6%, 21.1% and 25%.[29,49–51] The variations are likely subject to several factors including, but not limited to, settings and year of measurement. The outcomes in these patients is a subject of another assessment we conducted.

Regarding the risk by gender, our finding that females had a higher risk of experiencing TDF-associated decline in eGFR and RI is documented elsewhere.[16,52] The higher risk in females has been alluded to differences in the hormonal milieu associated with HIV.[53] Under normal physiological conditions, pre-menopausal females experience a slower decline in renal function than males, alluding the slower decline to the renal-protective effect of oestrogen.[54] However, HIV infection is associated with premature ovarian insufficiency and hypoestrogenaemia. The diminished endogenous oestrogen production has been associated with loss of oestrogen-related renal-protection.[55] On the other hand, during pregnancy, high oestrogen and progesterone concentrations are associated with increases in the GFR.[56] Perhaps this is why Lanagan *et al.,* and Myer *et al.,* did not find an increased risk of decline in eGFR amongst pregnant females receiving TDF-containing ART.[37,57] However, in our study, pregnancy was a risk factor for both decline in eGFR and RI, similar to findings by Mulubwa *et al.*[46] We are not sure of the reasons for this finding, but will follow it up in future studies.

Our finding that a high baseline eGFR was a risk factor for decline in eGFR is not new; it has been documented by others.[16,20,21,23–27] Nishijima *et al.,* explained that low body weights prior to initiation of ART and their corresponding low SeCr yielded pseudo normal baseline eGFR, which declined as the SeCr rose as a result of increases in body weight secondary to ART.[58] Another plausible explanation for this finding is HIV-related under-expression of TDF's renal transporters in the basement membrane of the proximal tubules. Kis *et al*., explained that HIV reduces the expression of ABCC2/MRP2 in the GIT of HIV positive ART naïve patients than in uninfected subjects.[59] Similarly, Pour and Piquette found that HIV reduced the expression of renal transporters in Mice.[60] Ghoneim *et al*., published similar findings on the expression of drug transporters on the placenta of HIV positive tag mice that were treated with endotoxin, compared with the HIV negative ones.[61] In this line of thought, HIV induced under-expression of TDF's renal transporters would result in reduced TDF secretion, reduced TDF concentration in the tubular cells, and reduced TDF-associated cellular damage. This would be the case for patients with more advanced HIV-related renal effects than others, which is also associated with an HIV associated reduction in eGFR. Our binary logistic regression results support this, as they indicate that a CD4 count >200 was associated with a significantly higher risk of experiencing decline in eGFR and new-onset RI. Koh and Kumar found a higher incidence of decline in eGFR amongst patients with lower baseline eGFRs,[18] but in a recent study we found that a low baseline eGFR was associated with more improvement than decline.[62]

Although patients in eGFR stage I were more predisposed to experiencing the decline in eGFR than lower eGFR stages, they were less susceptible to experiencing RI than patients in eGFR stage II.[28,63,64] However, patients in the eGFR stage I who had hyperfiltration, were more predisposed to RI, thus strengthening our subjective link between hyperfiltration and pre-diabetes or pre-hypertension in our patients, which conditions are related with increasing weight. However, the effect of weight was quite low. High glucose levels in plasma are associated with glomerular and tubular hypertrophy, which may result in fibrosis of the tubules and atrophy of the tubular lumen. Consequently, renal function is compromised.[65] Hypertension is associated with arterial stiffness and narrowing of the lumen, thus reducing blood supply to the kidneys. Decline in eGFR and new-onset RI are expected, when a nephrotoxic drug such as TDF is administered in patients undergoing these pathogenic processes.[66,28,64,67] All patients who experienced new-onset RI required dosage interval prolongation and dose adjustment for TDF and other renally excreted drugs, respectively. Unfortunately, we did not have data on the practice of dosage adjustment. In resource limited settings, where fixed dose

combinations are preferred, [68] single drug formulation may be difficult to come by when they are needed as in patients who experience new-onset RI. However, single TDF formulations are readily available in public health facilities in Namibia.

The main limitation of our study was the lack of a comparator regimen – non TDF-containing – as renal function assessments were only conducted for patients who received TDF-containing ART, in accordance with Namibia's ART guidelines.[69] The second limitation was the absence of data on co-morbidities and comedications that could influence renal function, apart from hyperfiltration which we linked to pre-diabetes and pre-hypertension. TDF is still a suspect drug, because there is evidence that TDF can accelerate the occurrence of renal impairment in susceptible patients.[8,70,71] The third limitation is that for pregnancy as a risk factor, we could not confirm whether the observed decline had happened during the pregnancy of after. The fourth limitation is that having a minority of patients with more than two tests, in addition to having test results at irregular times and varying endpoints was a challenge, especially when using cox-regression which requires the time variable. For sensitivity purposes, we conducted binary logistic regression analyses with and without the duration of follow-up. The findings that were generated by binary logistic regression analyses like the cox-regression analysis finding (Supplementary document). Some patients who were in eGFR stages from III downwards who experienced significant percentage declines, without change in stage, were not counted as experiencers of decline in eGFR. However, the declines they experienced were clinically important. Similarly, our focus on new-onset RI excluded patients who had pre-existing RI. Some of these experienced further decline in eGFR. Next, we will conduct studies on these cases, in addition to the cases of decline in eGFR and new-onset RI. Chart review will be the approach for the future study on these specific cases.

Conclusion

The incidence rate of decline in eGFR was relatively high in our cohort compared with other studies in sub-Saharan Africa, but the incidence rate of new-onset RI was relatively the same as that estimated in other studies. A high baseline eGFR, hyperfiltration, female gender, high body weight and pregnancy were risk factors for decline in eGFR and new-onset RI. TDF is safer for patients with normal and mildly reduced eGFRs. Prior to initiating TDF-containing ART renal function assessment is necessary, as this will identify patients at the extremes, including patients with hyperfiltration. Patients experiencing hyperfiltration should be initiated on non TDF-containing ART, as the risk of decline in eGFR leading to RI is increased in these patients. However, if the patients are coinfected with hepatitis-B, TDF-containing regimens are irreplaceable. Should TDF-containing ART be prescribed in patients with hyperfiltration, prompt monitoring of renal function is advised to identify patients who may need dosage adjustments or prolongation of the dosage interval to avoid accumulation of TDF and other renally excreted drugs. In resource limited settings, patients with hyperfiltration at baseline; and patients with high body weights but low baseline eGFRs should be screened for diabetes mellitus, and hypertension. Early identification and appropriate management of these comorbidities will likely prolong renal survival. Patient with hyperfiltration should be recognised as high-risk patients. The relationship between high body weights and low baseline eGFR, with low follow-up eGFRs invites screening for diabetes mellitus and hypertension. Screening for diabetes and cardiovascular diseases may be targeted for these patients. Although we did not have data on dosage adjustments, it is critical to mention that prompt monitoring of renal function will identify improvements in eGFR requiring increment in TDF's doses and doses of other renally excreted drugs, avoiding sub-therapeutic concentrations that would promote the emergence of resistance. More research is needed to explain the relationship between pregnancy and decline in eGFR and new-onset RI. Also, further research is required to study the renal function outcomes for cases of decline in eGFR and new-onset RI, including assessment of the interventions.

Key points
- Renal impairment can occur with or without significant decline in eGFR. Renal impairment is a more important indicator of nephrotoxicity than decline in eGFR per-se.

- Hyperfiltration is a risk factor for renal impairment in HIV infected patients. The health care worker should consider hyperfiltrating patients to be high-risk patients.
- TDF-containing ART should be avoided in patients with hyperfiltration, except when they are coinfected with hepatitis-B
- Renal function monitoring should be promptly implemented, especially in the first 12 to 18 months of TDF-containing ART to identify patients who will benefit from TDF dosage adjustments. This includes the experiencers of renal impairment and those whose eGFR has improved.
- Patients who do not experience improvement in eGFR after initiating ART included those who experience decline that may not meet specific criteria yet may be clinically important. Such patients are likely to benefit from screening for co-morbidities associated with renal disease to allow prompt therapy.

Conflicts of interest: None

References

1. Campos P, Ortiz A, Soto K. HIV and kidney diseases: 35 years of history and consequences. *Clin Kidney J*. 2016;9(6):772-781. doi:10.1093/ckj/sfw104

2. Brennan A, Evans D, Maskew M. Relationship between Renal Dysfunction, Nephrotoxicity and Death among HIV Adults on Tenofovir. *AIDS*. 2011;25(13):1603-1609. doi:10.1097/QAD.0b013e32834957da.Relationship

3. Röling J, Schmid H, Fischereder M. et al. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. *Clin Infect Dis*. 2006;42(10):1488-1495. doi:10.1086/503566

4. Mataranyika PA, Kibuule D, Kalemeera F, Kaura H, Godman B, Rennie T. et al. Liver enzyme elevations in a cohort of HIV/AIDS patients on first-line antiretroviral therapy in Namibia: Findings and implications. *Alexandria J Med*. 2017:doi:10.4172/2329-8731.1000170. doi:10.1016/j.ajme.2017.03.002

5. Kalemeera F, Mbango C, Mubita M, Naikaku E, Gaida R, Godman B. et al. Expert Review of Anti-infective Therapy Effect of changing from first- to second-line antiretroviral therapy on renal function : a retrospective study based on data from a single health facility in Namibia. *Expert Re*. 2016;7210(June):http://dx.doi.org/10.1016/j.ajme.2017.03.002. doi:10.1080/14787210.2016.1202759

6. Quesada P, Esteban L, Garcia J. et al. Incidence and risk factors for tenofovir-associated renal toxicity in HIV-infected patients. *Int J Clin Pharm*. 2015;37(5):865-872.

7. Baxi SM, Greenblatt RM, Bacchetti P. 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. doi:10.1097/QAD.0000000000000033

8. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB. et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat*. 2011:DOI: 10.1155/2011/354908. doi:10.1155/2011/354908

9. Bonjoch A, Echeverria P, Perez-Alvarez N. et al. Prospective Study to Assess Progression of Renal Markers after Interruption of Tenofovir due to Nephrotoxicity. *Biomed Res Int*. 2016:10.1155/2016/4380845. doi:10.1155/2016/4380845

10. Baxi SM, Scherzer R, Greenblatt RM. et al. Higher tenofovir exposure is associated with

longitudinal declines in kidney function in women living with HIV. *AIDS*. 2016;30(4):609-617. doi:10.1097/QAD.0000000000000958

11. Waheed S, Attia D, Estrella MM. et al. Proximal tubular dysfunction and kidney injury associated with tenofovir in HIV patients : a case series. *CKJ*. 2015;8(4):420-425. doi: 10.1093/ckj/sfv041. doi:10.1093/ckj/sfv041

12. Levey AS, Coresh J, Greene T. et al. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. *Ann Intern Med*. 2006;145(4):247-254.

13. Samuels R, Bayerri CR, Sayer JA, Price D., Payne A. B. et al. Tenofovir disoproxil fumarate-associated renal tubular dysfunction: Noninvasive assessment of mitochondrial injury. *AIDS*. 2017;(9):1297-1301. doi:10.1097/QAD.0000000000001466

14. Jafari A, Khalili H, Dashti-Khavidaki S. Tenofovir-induced nephrotoxicity: Incidence, mechanism, risk factors, prognosis and proposed agents for prevention. *Eur J Clin Pharmacol*. 2014;70(9):1029-1040. doi:10.1007/s00228-014-1712-z

15. Chaisiri K, Bowonwatanuwong C, Kasettratat 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):504-509. doi:10.2174/157016210793499259

16. Kyaw NTT, Harries AD, Chinnakali P. et al. Low incidence of renal dysfunction among HIV-infected patients on a tenofovir-based first line antiretroviral treatment regimen in Myanmar. *PLoS One*. 2015;10(8):1-11. doi:10.1371/journal.pone.0135188

17. Nishijima T, Kawasaki Y, Tanaka N. 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):1903-1910. doi:10.1097/QAD.0000000000000347

18. Koh HM, Kumar S. Tenofovir-induced nephrotoxicity: A retrospective cohort study. *Med J Malaysia*. 2016;71(6):308-312.

19. Coresh J, Turin TC, Matsushita K. et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA - J Am Med Assoc*. 2014;311(24):2518-2531. doi:10.1001/jama.2014.6634

20. Huang YS, Chan CK, Tsai MS. et al. Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients. *J Microbiol Immunol Infect*. 2017;50(5):595-603. doi:10.1016/j.jmii.2015.08.019

21. Pujari SN, Smith C, Makane A, et al. 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):doi:10.1186/1471-2334-14-173. doi:10.1186/1471-2334-14-173 10.1186/1471-2334-14-173.

22. Rasch MG, Engsig FN, Feldt-Rasmussen B. et al. Renal function and incidence of chronic kidney disease in HIV patients: a Danish cohort study. *Scand J Infect Dis*. 2012;44(9):689-696. doi:10.3109/00365548.2012.673730

23. Horberg M, Tang B, Towner W. et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2010;53(1):62-69. doi:10.1097/QAI.0b013e3181be6be2

24. Antoniou T, Raboud J, Chirhin S. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med*. 2005;6:284-290. doi:10.1111/j.1468-1293.2005.00308.x

25.   Mulenga L, Musonda P, Mwango A. et al. Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia. *Clin Infect Dis*. 2014;58(10):1473-1480. doi:10.1093/cid/ciu117

26.   Johnson DC, Chasela C, Maliwichi M, et al. et al. Tenofovir use and renal insufficiency among pregnant and general adult population of HIV-infected, ART-na??ve individuals in Lilongwe, Malawi. *PLoS One*. 2012;7(7):e41011. doi:10.1371/journal.pone.0041011. doi:10.1371/journal.pone.0041011

27.   Scherzer R, Estrella M, Li Y. et al. Association of Tenofovir Exposure with Kidney Disease Risk in HIV Infection. *AIDS*. 2012;26(7):867-875. doi:10.1097/QAD.0b013e328351f68f.Association

28.   Lapadula G, Bernasconi DP, Casari S. et al. Risk of chronic kidney disease among patients developing mild renal impairment during tenofovir-containing antiretroviral treatment. *PLoS One*. 2016;11(9):1-11. doi:10.1371/journal.pone.0162320

29.   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. *Trop Med Int Health*. 2015;20(4):518-526. doi:10.1111/tmi.12446

30.   Purswani M, Patel K, Kopp JB, Al E. et al. Tenofovir Treatment Duration Predicts Proteinuria in a Multiethnic United States Cohort of Children and Adolescents With Perinatal HIV-1 Infection. *Pediatr Infect Dis J*. 2013;32(5):495-500. doi:10.1097/INF.0b013e31827f4eff

31.   Fafin C, Pugliese P, Durant J. et al. Increased time exposure to tenofovir is associated with a greater decrease in estimated glomerular filtration rate in HIV patients with kidney function of less than 60 ml/min/1.73 m. *Nephron - Clin Pract*. 2012;120(4):c205-14. doi: 10.1159/000342377. doi:10.1159/000342377

32.   Salome T, Kasamba I, Mayanja BN. et al. The effect of Tenofovir on renal function among Ugandan adults on long-term antiretroviral therapy: a cross-sectional enrolment analysis. *AIDS Res Ther*. 2016;13(1):28. DOI 10.1186/s12981-016-0113-z. doi:10.1186/s12981-016-0113-z

33.   Nishijima T, Kawasaki Y, Mutoh Y. et al. Prevalence and factors associated with chronic kidney disease and end-stage renal disease in HIV-1-infected Asian patients in Tokyo. *Sci Rep*. 2017;7(14565.):doi: 10.1038/s41598-017-15214-x. doi:10.1038/s41598-017-15214-x

34.   Crum-Cianflone N, Ganesan A, Teneza-Mora N. et al. Prevalence and factors associated with renal dysfunction among HIV-infected patients. *AIDS Patient Care STDS*. 2010;24(6):353-360. doi:10.1089/apc.2009.0326

35.   Déti EK, Thiébaut R, Bonnet F, et al. Prevalence and factors associated with renal impairment in HIV-infected patients, ANRS C03 Aquitaine Cohort, France. *HIV Med*. 2010;11(5):308-317. doi:10.1111/j.1468-1293.2009.00780.x

36.   Boyd A, Miailhes P, Lascoux-Combe C. et al. Renal outcomes after up to 8 years of tenofovir exposure in HIV-HBV-coinfected patients. *Antivir Ther*. 2017;22(1):31-42. doi:10.3851/IMP3076

37.   Flanagan S, Barnes L, Anderson J, Barber T. The effect of tenofovir on renal function in HIV-positive pregnant women. *J Int AIDS Soc*. 2014;17:19694. doi:10.7448/ias.17.4.19694

38.   Corbell C, Katjitae I, Mengistu A. et al. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. *Pharmacoepidemiol Drug Saf*. 2012;21(4):407-414. doi:10.1002/pds.2252

39.   Ministry of Health and Social Services, Namibia. National Guideliens for Antiretroviral Therapy. 2010;(July).

40.   Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: Definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant*. 2012;27(12):4263-4272. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10b&NEWS=N&AN= 2012735768.

41.   Tonneijck L, Muskiet MHA, Smits MM, et al. Glomerular hyperfiltration in diabetes: Mechanisms, clinical significance, and treatment. *J Am Soc Nephrol*. 2017;28(4):1023-1039. doi:10.1681/ASN.2016060666

42.   Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. *Clin J Am Soc Nephrol*. 2015;10(3):382-389. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L602890184 %5Cnhttp://dx.doi.org/10.2215/CJN.03080314%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMB ASE&issn=1555905X&id=doi:10.2215%2FCJN.03080314&atitle=A+systematic+review+of+ glomerul.

43.   Trevisan R, Dodesini A. The Hyperfiltering Kidney in Diabetes. *Nephron*. 2017;136(4):277-280. doi:10.1159/000448183 LK - http://lh.cineca.it/Ccube/openclink.do?sid=EMBASE&sid=EMBASE&issn=22353186&id=do i:10.1159%2F000448183&atitle=The+Hyperfiltering+Kidney+in+Diabetes&stitle=Nephron& title=Nephron&volume=136&issue=4&spage=277&epage=280&aulast=Trevisan&aufirst=Ro berto&auinit=R.&aufull=Trevisan+R.&coden=&isbn=&pages=277-280&date=2017&auinit1=R&auinitm=

44.   Palatini P. Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant*. 2012;27(5):1708-1714. doi:10.1093/ndt/gfs037

45.   Chagnac A, Zingerman B, Rozen-Zvi B, Herman-Edelstein M. Consequences of glomerular hyperfiltration: The role of physical forces in the pathogenesis of chronic kidney disease in diabetes and obesity. *Nephron*. 2019;143(1):38-42. doi:10.1159/000499486

46.   Mulubwa M, Rheeders M, Fourie C, Viljoen M. Associations between plasma tenofovir concentration and renal function markers in HIV-infected women. *South Afr J HIV Med*. 2016;17(1). doi:10.4102/sajhivmed.v17i1.458

47.   Ng DK, Jacobson LP, Brown TT, et al. HIV therapy, metabolic and cardiovascular health are associated with glomerular hyperfiltration among men with and without HIV infection. *AIDS*. 2014;28(3):377-386. doi:10.1097/QAD.0000000000000094

48.   Algar FJ, Alvarez A, Aranda JL, Salvatierra A, Baamonde C, López-Pujol FJ. Prediction of early bronchopleural fistula after pneumonectomy: A multivariate analysis. *Ann Thorac Surg*. 2001;72(5):1662-1667. doi:10.1016/S0003-4975(01)03096-X

49.   Assaram S, Magula NP, Mewa Kinoo S, Mashamba-Thompson TP. Renal manifestations of HIV during the antiretroviral era in South Africa: A systematic scoping review. *Syst Rev*. 2017;6(1):1-11. doi:10.1186/s13643-017-0605-5

50.   Mpondo BCT, Kalluvya SE, Peck RN, et al. Impact of antiretroviral therapy on renal function among HIV-infected tanzanian adults: A retrospective cohort study. *PLoS One*. 2014;9(2):1-5. doi:10.1371/journal.pone.0089573

51.   Msango L, Downs JA, Kalluvya SE, et al. Renal dysfunction among HIV-infected patients starting antiretroviral therapy. *AIDS*. 2011;25(11):1421-1425. doi:10.1097/QAD.0b013e328348a4b1

52. 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):567-575. doi:10.1093/cid/cis937

53. Chang PY, Chien LN, Lin YF, Wu MS, Chiu WT, Chiou HY. Risk factors of gender for renal progression in patients with early chronic kidney disease. *Med (United States)*. 2016;95(30). doi:10.1097/MD.0000000000004203

54. Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. *Nephrol Dial Transplant*. 2006;21(9):2577-2582. doi:10.1093/ndt/gfl227

55. Karim R, Mack WJ, Kano N. et al. Gonadotropin and Sex Steroid Levels in HIV-infected premenopausal Women and Their Association with Subclinical Atherosclerosis in HIV-infected and - uninfected women in the womens Interagency HIV Study. *JCEM*. 2013;4(98).

56. Hussein W, Lafayette R. Renal function in normal and disordered pregnancy. *Curr Opin Nephrol Hypertens*. 2014;23(1):46-53. doi:10.1097/01.mnh.0000436545.94132.52.Renal

57. Myer L, Kamkuemah M, Kaplan R, Bekker LG. Low prevalence of renal dysfunction in HIV-infected pregnant women: Implications for guidelines for the prevention of mother-to-child transmission of HIV. *Trop Med Int Heal*. 2013;18(11):1400-1405. doi:10.1111/tmi.12194

58. Nishijima T, Komatsu H, Gatanaga H. 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. doi:10.1371/journal.pone.0022661. doi:10.1371/journal.pone.0022661

59. Kis O, Sankaran-Walters S, Hoque MT, Walmsley SL, Dandekar S, Bendayan R. HIV-1 alters intestinal expression of drug transporters and metabolic enzymes: Implications for antiretroviral drug disposition. *Antimicrob Agents Chemother*. 2016;60(5):2771-2781. doi:10.1128/AAC.02278-15

60. Ghoneim RH, Kojovic D, Piquette-Miller M. Impact of endotoxin on the expression of drug transporters in the placenta of HIV-1 transgenic (HIV-Tg) rats. *Eur J Pharm Sci*. 2017;102:94-102. doi:10.1016/j.ejps.2017.03.004

61. Pour NK, Piquette-Miller M. Endotoxin modulates the expression of renal drug transporters in HIV-1 transgenic rats. *J Pharm Pharm Sci*. 2018;21(1S):117s-129s. doi:10.18433/jpps30017

62. Kalemeera F, Godman B, Stergachis A, Rennie T. Effect of TDF-containing regimens on creatinine clearance in HIV patients in Namibia with a baseline CrCl <60ml/min; findings and implications. *Hosp Pract*. 2019:DOI: 10.1080/21548331.2020.1703438.

63. Morlat P, Vivot A, Vandenhende MA, Al E. Role of Traditional Risk Factors and Antiretroviral Drugs in the Incidence of Chronic Kidney Disease, ANRS CO3 Aquitaine Cohort, France, 2004-2012. *PLoS One*. 2013;8(6). doi:10.1371/journal.pone.0066223

64. Suzuki S, Nishijima T, Kawasaki Y, Al E. Effect of Tenofovir Disoproxil Fumarate on Incidence of Chronic Kidney Disease and Rate of Estimated Glomerular Filtration Rate Decrement in HIV-1–Infected Treatment-Naïve Asian Patients: Results from 12-Year Observational Cohort. *AIDS Patient Care STDS*. 2017;31(3):105-112. doi:10.1089/apc.2016.0286

65. Lopez-Parra V, Mallavia B, Egido J, Gomez-Guerrero C. *Immunoinflammation in Diabetic Nephropathy: Molecular Mechanisms and Therapeutic Options*.; 2012. doi:10.5772/34541

66. American Heart Association. How High Blood Pressure Can Lead to Kidney Damage or Failure.

67.   Mizushima D, Nguyen DTH, Nguyen DT, Al E. Tenofovir disoproxil fumarate co-administered with lopinavir/ritonavir is strongly associated with tubular damage and chronic kidney disease. *J Infect Chemother*. 2018;24(7):549-554. doi:10.1016/j.jiac.2018.03.002

68.   Godman B, McCabe H, D Leong T. Fixed dose drug combinations–are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries. *Expert Rev Pharmacoeconomics Outcomes Res*. 2020;20(1):1-26. doi:10.1080/14737167.2020.1734456

69.   Republic of Namibia Ministry of Health and Social Services. *National Guidelines for Antiretroviral Therapy*.; 2014.

70.   Kalemeera F, Mbango C, Mubita M, Al E. Effect of changing from first- to second-line antiretroviral therapy on renal function: a retrospective study based on data from a single health facility in Namibia. *Expert Rev Anti Infect Ther*. 2016;14(8):777-783. doi:10.1080/14787210.2016.1202759

71.   Venter W, Feldman C, Fabian J. An overview of tenofovir and renal disease for the HIV-treating clinician. *South Afr J HIV Med*. 2018;19(1):1-8. https://sajhivmed.org.za/index.php/hivmed/article/view/817/1217.