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RISK FACTORS FOR TENOFOVIR RENAL TOXICITY: IMPACT OF PRIOR USE OF STAVUDINE AND CO-MEDICATIONS AMONG PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ATTENDING COMPREHENSIVE CARE CLINIC AT KENYATTA NATIONAL HOSPITAL, KENYA

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ABSTRACT

Objective: **To evaluate the incidence of and risk factors for nephrotoxicity in HIV patients on tenofovir (TDF)-based antiretroviral regimens.**

Design, Setting and Study participants: **This was a four-arm retrospective cohort study among 396 adult patients receiving treatment between January 2008 and March 2010 at the Kenyatta National Hospital, Kenya.**

Interventions and main outcome measures: **Patients were classified as being on TDF- or D4T-based regimens, those who switched therapy and those on other regimens. Serum creatinine levels and renal creatinine clearance were used to monitor renal function.**

Results: **Baseline prevalence of impaired renal function was 19.9% (95% CI: 16.3 – 24.2), the incidence was 0.5% (95% CI: 0.4 – 0.7) and the cumulative incidence was 13.5%. Patients who switched regimens had the highest cumulative incidence (19.1% (95% CI: 12.3 – 28.5).**

The incidence of nephrotoxicity (creatinine clearance < 60 mL/min) was higher in patients on TDF-based regimens (adjusted HR 2.62 (96% CI: 1.01 – 6.79; p= 0.048). Other risk factors were: age above 40 years (adjusted HR 3.07 (95% CI: 1.48 – 6.36; p = 0.002), weight below 65 kilograms (adjusted HR = 7.53 (95% CI: 2.75 – 20.63); p<0.001), WHO HIV/AIDS Stage IV (adjusted HR 4.13 (1.12 –

15.27; p = 0.034); hypertension (adjusted HR = 4.56 (0.98 – 21.21; p = 0.053); amphotericin B (adjusted HR 50.07 (6.90 – 363.42); p= 0.001); and opportunistic infections (adjusted HR = 0.40 (0.16 – 0.96); p = 0.042).

Conclusion: **Tenofovir nephrotoxicity is exacerbated by concurrent amphotericin B and efavirenz.**

INTRODUCTION

Globally, an estimated 37.9 million people are infected with HIV/AIDS and close to 1.7 million new infections occur each year (1). Locally, about five percent of Kenyan adults aged 15 to 49 years have HIV (2). Nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI) or integrase inhibitors, comprise first line treatments for HIV/AIDS. NRTIs include tenofovir disoproxil fumarate (TDF), lamivudine (3TC), emtricitabine (FTC), Zidovudine (AZT) and Stavudine (D4T). Use of D4T has diminished due to long term irreversible side effects especially lipoatrophy and peripheral neuropathy. Efavirenz (EFV) and Nevirapine (NVP) are the main NNRTIs while integrase inhibitors are exemplified by dolutegravir (DTG) and raltegravir (RAL) (3).

Patients receiving newer antiretroviral (ARV) regimens are often not treatment naïve. As a result, these patients may have a higher risk of developing renal disease due to cumulative drug-induced toxicity or advanced HIV disease. Studies have shown comparable efficacy and varying adverse effect profiles of TDF and D4T (4-6).

Adverse events of ARVs have been widely studied in high-income countries with little data emerging from low-income countries. Such data may, therefore, not be applicable to the African population because of substantial differences in genetic profiles, nutritional status and co-morbidities. It is, therefore, important to examine the incidence of renal disease in patients using ARVs in African populations as they may be particularly vulnerable to ARV-induced nephrotoxicity. The objective of this study was to measure the incidence of nephrotoxicity in patients receiving TDF and to examine the effects of switching regimens and co-medications. Risk factors for renal toxicity were identified.

MATERIALS AND METHODS

Ethical considerations: Study ethical approval was granted by the Kenyatta National Hospital-University of Nairobi (KNH-UON) Research and Ethics Committee (P393/11/2010). Informed consent was not required since study information was abstracted from patient files.

Study design: This was a four-arm analytic retrospective cohort study. One study arm consisted of treatment- naïve patients on TDF-based regimens. The second arm had patients on D4T-based regimens. The third arm consisted of patients who had been switched from D4T-based to TDF-based regimens. The fourth arm had patients neither on TDF nor D4T.

Study Site and Population: The study was conducted at the Comprehensive Care Center (CCC) of Kenyatta National Hospital, the largest referral hospital in Eastern Africa, among adult patients who received TDF- and D4T-based HAART regimens between January 2008 and March 2010. Data was collected retrospectively from the time the individual patients started treatment until December 2010.

Inclusion and Exclusion criteria: Adult patients (≥ 18 years) on a TDF- and/or D4T-based regimen between January 2008 and March 2010 were included in the study. Incomplete

records and pregnancy led to exclusion from the study.

Sampling and data collection: The planned sample size was 187 patients per study arm (748 for four arms) to enable the detection of a 5% difference in the incidence of nephrotoxicity across the study arms with 80% power (7). About half of the files within the study period were randomly selected from the computerized daily activity register and information abstracted from eligible records regarding patient demographics, laboratory and clinical data, antiretroviral drug regimen, concurrent medications and co-morbidities.

Case definition: Creatinine clearance (CrCL) was calculated using the Cockroft-Gault formula (8). A cut-off value of 60 mL/min was used to classify patients into those with renal insufficiency/nephrotoxicity (<60mL/min) and relatively normal renal function (≥ 60 mL/min) (9).

Data management and analysis: Patient files were serialized randomly and abstracted data entered daily into a Microsoft Excel spreadsheet. Data was examined at the end of every data entry session and any inconsistencies rectified by verifying information from the patient files. Data analysis was performed using SPSS software (version 12.0) and STATA (Intercooled version 13.0). The primary outcome of interest was nephrotoxicity while the predictor variables included patient demographics, baseline CD4 count, comorbidities, concomitant drugs, duration of treatment, body mass and previous experience with ART. Descriptive data analysis was carried out on all variables. Baseline characteristics of the study arms were compared using Student's t-test, Mann Whitney and Pearson's Chi-squared tests. Time to the development of nephrotoxicity was compared across arms using the Log rank test. Cox regression modeling was used to control for confounding and to determine the most important risk factors for nephrotoxicity. Model-building was done using a forward stepwise approach. The level of significance was set at 0.05.

RESULTS

Baseline characteristics of the study population: A total of 3235 patients were started on HAART within the study period. From 1420 randomly selected files, 396 records met the inclusion criteria (Figure 1). The targeted sample size in each arm (187) could not be achieved particularly where patients had switched from first line regimens as well as for those on D4T- based regimens as this drug had been discontinued. Few patients had switched therapy to a non-TDF based regimen, only 31 participants could be recruited in this arm. The desired sample size was almost achieved among participants on TDF-based regimens but most records were incomplete, failing to meet the inclusion criteria.

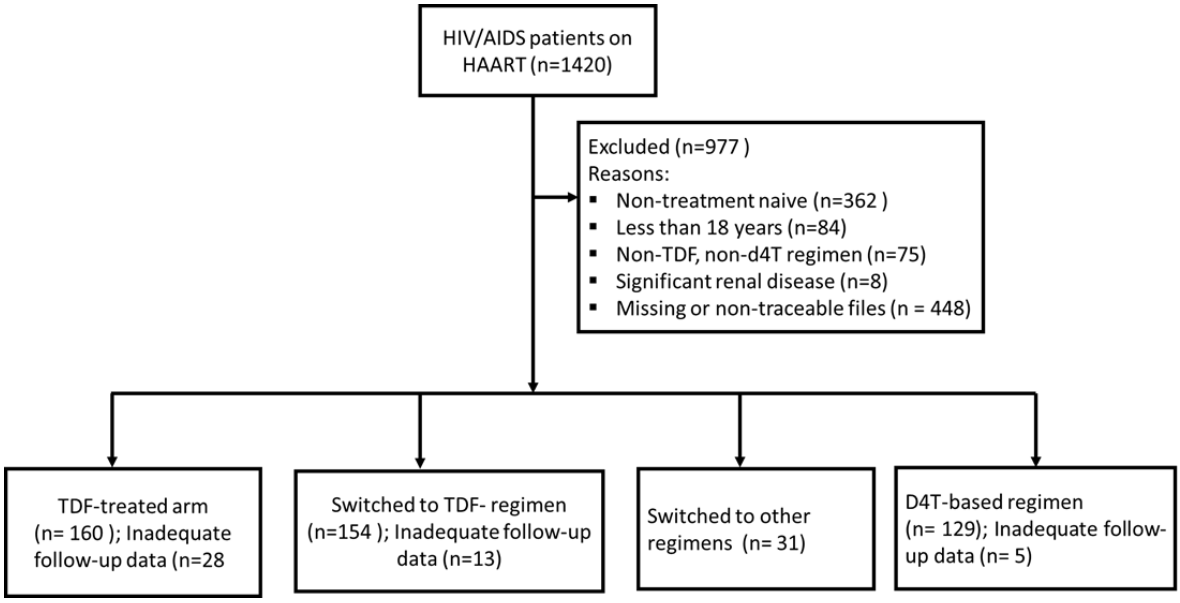

Figure 1: Consort flow diagram of patient cohort eligibility and reasons for exclusion

Baseline characteristics for study patients are summarized in **Table 1**. Most patients were female (62.1%) and the median age was 37 (range 18 - 63) years. On starting therapy, 149 (37.6%) patients had a CD4 cell count less than 100 cell/μL and the median bodyweight was 60 (range 34 - 121) kilograms. Most patients (38.6%) started treatment when at WHO stage III of disease. The prevalence of most co-morbidities was less than 10% except for respiratory tract infections (13.4%) and tuberculosis (26.0%). Frequent concomitant medications were non-steroidal anti-inflammatory medicines (NSAIMs) (34.1%) and antibiotics (40.7%). Less than 10.0% of the patients were on systemic acyclovir and amphotericin B.

Table 1

Baseline characteristics of the study population

Baseline Characteristics	TDF (N=132)	D4T to TDF (N=110)	Others (N=31)	D4T arm (N=123)	Total	P value
Female, n (%)	75 (56.8%)	79 (71.8%)	21 (67.7%)	71 (57.7%)	246 (62.1%)	0.060
Median age in years (IQR)	39 (33 – 45)	38 (31 – 44)	38 (29 – 45)	35 (29 – 40)	37 (31 – 43)	**0.002**
Age >40 years, n (%)	51(38.6%)	38 (34.5%)	14 (45.2%)	26 (21.1%)	129 (32.6%)	**0.008**
Duration of HIV infection months (IQR)	1.5 (0.5-11.8)	1.0 (0.4 - 4.1)	1.4(0.5 - 9.6)	1.2 (0.6-5.1)	1.3(0.5-6.3)	0.128
Duration of HIV infection ≥6 months, n (%)	43 (32.6%)	23 (20.9%)	9 (29.0%)	28 (22.8%)	103 (26.0%)	0.153
Median baseline CD4 count (IQR)	126 (46 - 258)	165 (80 - 262)	159 (65 - 284)	148 (70 - 241)	148 (60 – 251)	0.353

CD4 count < 100 cell/mm^3, n (%)		59 (44.7%)	34 (30.9%)	13 (41.9%)	43 (35.0%)	149 (37.6%)	0.136
Median baseline weight (kg) (IQR)		60 (53 – 69)	58 (51 – 68)	66 (59 – 78)	60 (53 – 68)	60 (53 – 69)	**0.025**
Weight < 65 kilograms, n (%)		82 (62.1%)	75 (68.2%)	14 (45.2%)	83 (67.5%)	254 (64.1%)	0.091
Active OI, n (%)		80 (60.6%)	58(52.7%)	18 (58.1%)	60 (48.8%)	216 (54.5%)	0.272
Baseline WHO stage, n (%)	I	30 (22.7%)	20 (18.2%)	5 (16.1%)	25 (20.3%)	80 (20.2%)	0.740
	II	28 (21.2%)	33 (30.0%)	12 (38.7%)	35 (28.5%)	108 (27.3%)	
	III	52 (39.4%)	43 (39.1%)	10 (32.3)	48 (39.0%)	153 (38.6%)	
	IV	22 (16.7%)	14 (12.7%)	4 (12.9%)	15 (12.2%)	55 (13.9%)	
Co-morbidities, n (%):							
Diabetes Mellitus		4 (3.3%)	1 (0.9%)	1 (3.2%)	3 (2.4%)	9 (2.3%)	0.705
Hypertension		8 (6.1%)	6 (5.5%)	4 (12.9%)	0 (0.0%)	18 (4.5%)	**0.008**
Malignancy		3 (2.3%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	5 (1.3%)	0.345
HBV		4 (3.0%)	3 (2.7%)	0 (0.0%)	3 (2.4%)	10 (2.5%)	0.810
Respiratory Tract Infection		13 (9.8%)	14 (12.7%)	4 (12.9%)	22 (17.9%)	53 (13.4%)	0.305
Tuberculosis		46 (34.8%)	26(23.6%)	4 (12.9%)	27 (22.0%)	103 (26.0%)	**0.023**
Medications, n (%):							
Cotrimoxazole		107 (100%)	80 (98.8%)	28 (100%)	108 (95.6%)	323 (98.2%)	**0.074**
NSAIDs		42 (31.8%)	46 (41.8%)	12 (38.7%)	35 (28.5%)	135 (34.1%)	0.154
Acyclovir		7 (5.3%)	11 (10.0%)	5 (16.1%)	12 (9.8%)	35 (8.8%)	0.221
Amphotericin B		5 (3.8%)	0 (0.0%)	2 (6.5%)	4 (3.3%)	11 (2.8%)	0.152
Antibiotics		44 (33.3%)	44 (40.0%)	15 (48.4%)	58 (47.2%)	161 (40.7%)	0.118
Smoking, n (%)		14 (10.6%)	6 (5.5%)	0 (0.0%)	6 (4.9%)	26 (6.6%)	0.090
Alcohol consumption, n (%)		24 (18.2%)	17 (15.5%)	6 (19.4%)	15 (12.2%)	62 (15.7%)	0.556
Baseline creatinine (umol) (IQR)		86 (73 – 99)	85 (70 – 100)	84 (73 – 100)	84 (68 – 97)	85 (71 – 99)	0.462
Creatinine clearance (ml/min) (IQR)		81 (60 – 100)	83 (65 – 97)	86 (68 – 101)	81 (69 – 110)	83(65 – 102)	0.418
ARV regimens, n (%)	NVP	19 (14.4%)	58 (52.7%)	8 (25.8%)	82 (66.7%)	167 (42.2%)	**<0.001**
	EFV	113 (85.6%)	52(47.3%)	23 (74.2%)	41(33.3%)	229 (57.8%)	

TDF: Tenofovir; D4T: Stavudine; EFV: Efavirenz; NVP: Nevirapine; OI: Opportunistic infections; NSAIDs: Non-steroidal anti-inflammatory drugs.

More patients were on D4T- (123, 31.1%) and TDF- (132, 33.3%) based regimens than those who switched treatment from D4T- to TDF- based regimens (110, 27.8%) and others (31, 7.8%). More women switched treatment from D4T to TDF (71.8%, p=0.06) but the TDF and D4T study arms had a more balanced gender distribution (56.8% and 57.7%, respectively).

EFV and NVP were the frequent NNRTIs in the TDF- (85.6%, p<0.01) and D4T- (66.7%, p<0.001) containing treatment arms, respectively.

Baseline Renal Dysfunction:

The median baseline serum creatinine level and creatinine clearance were 85 μmol (range 34 – 282) and 83 ml/min (interquartile range (IQR) 71 – 99), respectively. Renal dysfunction (CrCL<60 mL/min) did not differ across study arms (**Table 1**).

Incidence and Risk Factors for Nephrotoxicity in Patients with Normal Baseline Renal Function:

The nephrotoxicity incidence rate was 5.0 cases per 1000 person-months (95% CI: 4 – 7) while the cumulative incidence was 13.5%. The incidence of nephrotoxicity was highest among patients using TDF. Patients who had switched from D4T to TDF had higher cumulative incidence of renal toxicity than those on TDF alone. However, the incidence rate was lower compared to those who were initiated on TDF at the start of ARV therapy (**Table 2**).

Table 2

Comparison of Incidence rate and Cumulative incidence of nephrotoxicity in patients treated with TDF- and D4T- based HAART regimens at Kenyatta National Hospital, Kenya

Type of regimen	**N**	**Events (cumulative follow up in months)**	**%Cumulative Incidence** (95 % CI)	**Incidence rate** Cases per 1000 person-months (95% CI)
TDF	98	15 (1674)	15.3 (9.5 – 23.8)	9.0 (5 - 15)
D4T	105	11 (2969)	10.5 (6.0 – 17.8)	4.0 (2 – 7)
D4T switch to TDF	89	17 (2948)	19.1 (12.3 – 28.5)	6.0 (4 - 9)
Miscellaneous regimens	25	1 (521)	4 (0.7 – 19.5)	2.0 (0.5 - 11)
Overall	317	44 (8112)	13.5	5.0 (4 – 7)

The survival curves depicting time to develop nephrotoxicity are presented in Figure 2. The Log Rank test showed a statistically significant difference in the survival probabilities across the arms (p = 0.028). Notably, patients on TDF-based regimens alone developed nephrotoxicity faster than those in other arms (Table 2). For patients who were switched from D4T- to TDF-based regimen, nephrotoxicity occurred as late as 5 to 6 years after starting treatment (Figure 1).

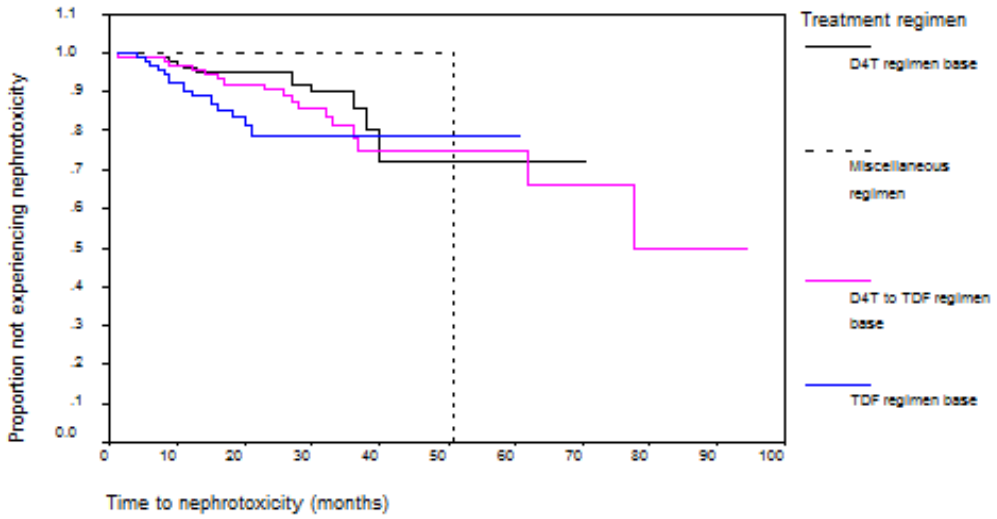

Figure 2: Survival curves for development of nephrotoxicity

Risk factors for nephrotoxicity

The Cox proportional hazard regression model (for censored responses) was used to identify variables predictive of nephrotoxicity. Bivariable and multivariable analyses were conducted yielding results as depicted in Table 3.

Table 3

Risk factors for nephrotoxicity among patients on HAART with normal baseline renal function at Kenyatta National Hospital

Variables	Bivariable analysis		Multivariable analysis	
	Crude		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
TDF regimen	2.92 (1.31 - 6.55)	**0.009**	2.62 (1.01 – 6.79)	**0.048**
D4T to TDF regimen	1.42 (0.66 - 3.09)	0.371	1.40 (0.52 – 3.73)	0.503
Miscellaneous regimen	0.59 (0.08 - 4.63)	0.619	0.34 (0.04 – 3.29)	0.353
Age at start of HAART >40 years	2.20 (1.22 - 3.99)	**0.009**	3.07 (1.48 – 6.36)	**0.002**
Male	1.15 (0.63 - 2.10)	0.641	0.94 (0.43 – 2.04)	0.876
Duration of HIV infection ≥ 6 months	1.04 (0.54 - 1.99)	0.914	1.25 (0.59 – 2.64)	0.558
Baseline CD4 count < 100 cell/mm^3	1.86 (1.02 -3.39)	**0.045**	1.38 (0.66 – 2.85)	0.392
Baseline weight < 65 kg	3.24 (1.44 – 7.29)	**0.004**	7.53 (2.75 – 20.63)	**<0.001**
Opportunistic infection	1.11 (0.59 - 2.06)	0.750	0.40 (0.16 – 0.96)	**0.042**
WHO stage IV	2.94 (1.11 - 7.77)	**0.030**	4.13 (1.12 – 15.27)	**0.034**

WHO stage III	1.43 (0.61 - 3.36)	0.412	1.89 (0.59 – 6.08)	0.287
WHO stage II	1.24 (0.49 - 3.12)	0.650	2.29 (0.77 – 6.82)	0.138
Diabetes	1.60 (0.22 - 11.70)	0.646	1.39 (0.14 – 13.84)	0.781
Hypertension	2.15 (0.66 - 7.02)	0.203	4.56 (0.98 – 21.21)	**0.053**
Hepatitis B virus	2.58 (0.35 - 18.92)	0.351	0.78 (0.05 – 13.43)	0.866
Respiratory tract infection	1.49 (0.65 - 3.38)	0.345	2.21 (0.87 – 5.60)	0.096
Tuberculosis	1.73 (0.86 - 3.49)	0.127	1.99 (0.82 – 4.82)	0.127
Use of Efavirenz	2.98 (1.51 - 5.88)	**0.002**	1.75 (0.80 – 3.87)	0.163
Use of NSAID	1.25 (0.67 - 2.33)	0.488	1.50 (0.70 – 3.20)	0.298
Use of Acyclovir	0.29 (0.04 - 2.08)	0.216	0.44 (0.05 – 3.65)	0.446
Use of Amphotericin B	7.14 (1.71 - 29.77)	**0.007**	50.07 (6.90 – 363.42)	**<0.001**
Use of Antibiotics	1.15 (0.62 - 2.12)	0.659	0.86 (0.43 – 1.71)	0.664
Cotrimoxazole	1.27 (0.61 – 2.67)	0.528	1.78 (0.74 – 4.28)	0.194
Hepatotoxicity	1.26 (0.17 - 9.18)	0.819	2.86 (0.35 – 23.62)	0.329
Smoking	2.27 (0.81 - 6.39)	0.120	0.98 (0.19 – 5.15)	0.985
Alcohol consumption	1.63 (0.78 - 3.40)	0.192	1.51 (0.56 – 4.04)	0.415
Neuropathy	1.00 (0.45 - 2.25)	0.996	1.08 (0.40 – 2.92)	0.881
Lipodystrophy	1.12 (0.58 - 2.18)	0.737	1.22 (0.47 – 3.19)	0.680

After adjusting for confounding, the most important risk factors for developing nephrotoxicity were: use of a TDF-based regimen, baseline age above 40 years, weight less than 65 kg, WHO HIV/AIDS stage IV at the start of treatment, hypertension and use of Amphotericin B. Hepatotoxicity was an excellent predictor for renal dysfunction and its effects could not be modeled because of collinearity. Patients on TDF had a 2.62-fold risk of developing nephrotoxicity as compared to those on a D4T-based regimen (adjusted HR=2.62; 95% CI: 1.01– 6.79; p=0.048). The risk for developing nephrotoxicity was 3.07 (adjusted HR=3.07; 95% CI: 1.48 – 6.36; p=0.002) and 7.53 (adjusted HR=7.53; 95% CI: 2.75 – 20.63; p<0.001) times greater for patients aged > 40 years and those weighing below 65 kg, respectively. Moreover, while the use of amphotericin B was significantly associated with nephrotoxicity (adjusted HR=50.1; 95% CI: 6.90 – 363.42; p<0.001), the significantly increased nephrotoxic risk of EFV compared to NVP (unadjusted HR 2.98 (1.51 - 5.88; p = 0.002) was lost upon adjusting for confounding.

Other adverse reactions to ARVs

The incidence of hepatotoxicity, neuropathy and lipodystrophy was compared across study arms **(Table 4**).

Table 4

Comparison of the incidence of hepatoxicity, neuropathy and lipodystrophy in patients on TDF- and D4T- based regimens at Kenyatta National Hospital

	TDF (N=132)	D4T to TDF (N=110)	Others (N=31)	D4T arm (N=123)	Total	P-value
Hepatotoxicity, n (%)	3 (2.3%)	3 (2.7%)	0 (0.0%)	4 (3.3%)	10 (2.5%)	0.772
Neuropathy, n (%)	13 (9.8%)	30 (27.3%)	6 (19.4%)	12 (9.8%)	61 (15.4%)	**<0.001**
Lipodystrophy, n (%)	3 (2.3%)	58 (52.7%)	8 (25.8%)	11 (8.9%)	80 (20.2%)	**<0.001**

Patients who had switched treatment from D4T to TDF had the highest incidence of peripheral neuropathy (27.3%) and lipodystrophy (52.7%) ($p<0.001$) while the TDF-containing treatment arm had the lowest incidence of lipodystrophy (2.3%, $p<0.001$) and neuropathy (9.8%).

DISCUSSION

Existence of renal disease before the start of HAART is quite common among HIV-infected patients. The prevalence of baseline renal dysfunction in this cohort (19.9%) was much higher than in a US cross-sectional study (3%) (10) and a prospective cross-sectional study in Kenya (11.5%) (9). The US study population comprised mostly of African Americans originally from West Africa and, therefore, may have characteristics which differ from those of Eastern Africans. A Ugandan cross-sectional study (11) reported a baseline renal dysfunction prevalence similar to the current study (20%) probably due to comparable proportions of patients with advanced HIV disease (12).

A large US cohort study among HIV-infected outpatients reported a lower incidence of nephrotoxicity than our study: there were 21 (3.5%) and 12 (2.3%) patients in the TDF-exposed and TDF-unexposed groups (13). This observation could be related to differences in baseline CD4 cell count and renal dysfunction cut-off profiles between the studies.

Weight as a risk factor for renal disease should be interpreted cautiously since creatinine production is determined primarily by muscle mass and diet (14). Patients on HAART tend to gain weight over time and, additionally, renal function declines yearly at a rate of 1% beginning from the 4th decade of life (15).

Upon bivariable analysis, EFV was observed to be a risk factor for developing renal disease. This could be explained by the disproportionately large number of patients on TDF who received EFV rather than NVP. This regimen was selected so as to either allow for once-daily ART dosing with improved compliance or to accommodate the use of rifampicin in patients requiring anti-TB co-treatment. As observed in a cohort study in Zambia, patients on NVP had a lower incidence of renal disease (16). In contrast, a randomised clinical trial in Thailand found a positive association between receiving TDF-NVP-based therapy and poor renal outcomes after 3-6 months of switching from D4T to TDF (17). The comparator group in the study was patients receiving TDF-EFV-based treatment. The study recruited a small sample size of 28 patients on EFV- and 34 patients on NVP-treatment regimens and employed more sensitive measures of renal dysfunction including estimated glomerular filtration rate, hypophosphatemia and proteinuria.

The association of amphotericin B with nephrotoxicity concurs with results of a prospective observational study in Kenya which found that 58.6% of AIDS patients on amphotericin B had a two-fold increase in the creatinine levels from baseline while 38.6% of patients experienced a rise in serum creatinine of at least 50% (18).

In our study, TDF was more nephrotoxic than D4T, a finding that differs from reports by others who established no association between the use of TDF versus other NRTIs and the decline in renal function (19). The aforementioned study found that age above 45 years, baseline CD4 cell counts of less than 200 cells/mL, hypertension and the use of protease inhibitors with ritonavir-boosting (PI/r) were associated with renal toxicity.

Despite offering useful insights, this study has some limitations. First, it was not possible to rigorously test for the effects of EFV and NVP on renal function due to the insufficient numbers obtained in each treatment stratification. This, however, was not part of the study objectives and we suggest that more studies should be done in this area. The absence of HIV viral RNA load data, a known risk factor for chronic kidney disease, also limited the analysis of this important clinical indicator. Similarly, data was unavailable regarding other key risk factors such as ethnicity and genetic polymorphisms. The desired sample size for each arm was not achieved since most patients' files had incomplete follow-up data. Two arms were particularly under-presented as the treatment guidelines required that patients be put on TDF-based regimens. There were very few patients who had switched therapy to a non-TDF based regimen. As D4T had been discontinued, very few patients were on this regimen. Nonetheless, the study was sufficiently powered to detect increased renal toxicity amongst patients on TDF-based regimens.

CONCLUSION

This study found that renal dysfunction in HIV/AIDS patients who are starting therapy is quite common, occurring in about 1 in every 5 patients. The incidence of nephrotoxicity due to first-line TDF-based HAART is significantly greater than that attributed to D4T-based therapy, probably due to prior D4T-induced renal toxicity. High risk groups include patients with age greater than 40 years, weight less than 65 kg, those on potentially nephrotoxic medications and CD4 cell counts less than 100 cells/μL. The influence of EFV on TDF-induced nephrotoxicity requires further investigation.

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