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Effect of Tenofovor Diproxil Fumarate on Renal Function and Urinalysis Abnormalities in HIV-Infected Cameroonian Adults

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Abstract. In Sub-Saharan Africa, the prevalence of HIV-associated kidney diseases is as high as 53.3%. Combined antiretroviral treatment (cART), especially tenofovir disoproxil fumarate (TDF), is known to be nephrotoxic. We undertook this cross-sectional study conducted in 2015 at the Regional Hospital Limbe in the Southwest Region of Cameroon to determine the prevalence of renal dysfunction and its correlates among treatment-experienced HIV-infected patients on TDF and treatment-naïve patients. In April 2016, a follow-up was performed on those who had been treatment-naïve and were started on cART after enrolment in the study. We compared 119 patients on TDF-containing regimens with 47 treatment-naïve patients. Proteinuria was significantly more prevalent, and creatinine was significantly higher among treatment-naïve patients than among those on treatment (52.2% versus 26.1%; $P = 0.003$ and $P = 0.009$, respectively). The proportion of patients with an estimated glomerular filtration rate (eGFR) < 60 mL/minute was significantly higher among treatment-naïve patients than among those on TDF treatment (40.4% versus 24.4%; $P = 0.041$). Treatment-naïve patients displayed an improvement in creatinine levels and eGFR after 6 months of treatment. To the best of our knowledge, this is the first study to investigate the impact of TDF on renal parameters in Cameroon. TDF appears to be safe and does not appear to be a significant cause of renal impairment. However, renal parameters should be monitored regularly, as recommended by the guidelines.

INTRODUCTION

In Sub-Saharan Africa, the prevalence of HIV-associated kidney diseases ranges from 6% to 53.3%. HIV-associated nephropathy is the most common HIV-related renal pathology.[1–3] HIV-infected patients naïve to combined antiretroviral treatment (cART) show abnormalities in up to 41% of urinalyses, and, depending on the method used for estimating the glomerular filtration rate (GFR), up to 42% present with renal failure.[4,5] Alongside many other factors, some of the components of cART itself, including atazanavir, didanosine, indinavir, lopinavir/ritonavir, and especially tenofovir disoproxil fumarate (TDF), are known to be nephrotoxic. Although data from clinical trials indicate a low incidence of serious renal adverse effects,[6–8] cohort studies have linked TDF to a decreased estimated GFR (eGFR), proximal tubular dysfunction, proteinuria, chronic kidney disease, and increased mortality.[9–19]

TDF has formed as a part of the first-line treatment of HIV in Cameroon since 2014. Although the guidelines recommend the screening of newly diagnosed HIV patients for kidney disease via urinalysis and estimation of renal function, renal investigations are not systematically performed in most parts of Sub-Saharan Africa.[20,21] This hampers the early detection of kidney involvement and the implementation of measures that prevent or mitigate kidney disease. Quantitative data on renal disease in HIV-infected patients may help to prevent further renal damage in this population, but few African studies to date have investigated renal function among patients on cART and compared it with that of treatment-naïve patients.[1,2,22–25]

Against this background, we undertook this study to determine the prevalence of renal dysfunction and its correlates among treatment-experienced HIV-infected patients on TDF and treatment-naïve patients.

MATERIALS AND METHODS

This was a cross-sectional study with a 1-month enrolment period (August to September 2015) conducted at the Regional Hospital Limbe in the Southwest Region of Cameroon. In 2015, the HIV Day Clinic of this hospital provided care to about 3,100 HIV-positive patients, and during the month of enrolment saw between 30 and 40 new HIV infections. Study participants were recruited from among the HIV-positive adult patients from the HIV Day Clinic. To be eligible for inclusion, patients had to be HIV-positive, either treatment-naïve or on cART, and aged 18 years or more. In April 2016, a long-term follow-up was performed on those who had been treatment-naïve before the study and were started on cART after enrolment in the study.

Data collection and laboratory testing. Clinical and laboratory data for each patient were recorded using a predesigned questionnaire. Along with age and gender, clinical data including weight, height, blood pressure, medical history, stage of HIV infection (the World Health Organization [WHO] classification), ongoing treatment, and history of tobacco and drug or alcohol abuse were recorded. The laboratory parameters recorded included urinary dipstick results, serum creatinine levels, and CD4 counts. Urinary dipstick tests were performed with Combur[10] Test® M (Cobas, Roche, Germany). Urinary pH, specific gravity and glucose were not taken into consideration. Serum creatinine was analyzed using the Jaffé reaction without deproteinization (Creatinine LR liquid reagent, SGMItalia, Rome, Italy), and serum fasting glucose was analyzed using the colorimetric enzymatic method GOD-POD (Glucose LR liquid reagent, SGMItalia). A Mindray BA-88A

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analyser (Shenzen Mindray Bio-Medical Electroics Co., Ltd., China) was used for both parameters. CD4 counts were performed using a BD FACS Count™ (BD Biosciences Clontech ware, Discovery Labware, Immunocytometry Systems Pharmingen, San Jose, CA). All specimens were analyzed in the Regional Hospital Limbe laboratory as a part of the routine laboratory workup.

The estimated glomerular filtration rate (eGFR; mL/minute) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD EPI) in accordance with the Kidney Disease Improve Global Outcome guidelines.[26] Diagnosis of proteinuria was based on a urinary dipstick of at least 1+ (30 mg/dL or more). The kidney size and structure were analyzed by ultrasound, and renal echogenicity grading was performed as described by Garko et al.[27] (Grade 0–normal, the renal cortex is slightly less echogenic than the liver; Grade I–renal cortex is of the same echogenicity with the liver; Grade II–renal cortex is mildly to moderately more echogenic than the liver, some loss of corticomedullary distinction; Grade III–renal cortex is severely echogenic, complete loss of corticomedullary distinction).

All treatment-naïve patients were put on cART in 2015. After enrolment into the study in April 2016, these patients were followed up, undergoing urinalysis, CD4 cell count, creatinine, and eGFR testing.

Ethics. Participation was voluntary and all participants provided informed written consent. The study was approved by the Ethics Committee of the University of Rostock, Germany (A 2015-0090), and by the Ethics Committee of the Regional Hospital Limbe in Cameroon, in accordance with the Declaration of Helsinki.

Statistical analysis. Statistical analysis was performed using the IBM® SPSS® Statistics 22.0 software package. Data are expressed as frequencies or proportions (%) for categorical variables and as mean ± standard deviation (SD) for continuous variables or, if skewed, as median and quartiles Q1 and Q3.

Differences in continuous variables between treatment-naïve patients and patients on treatment were compared using the t-Test (or Mann–Whitney *U* test for non-normality). Variables relating to a category were compared using the Pearson χ^2 or Fisher's exact test for 2 × 2 tables; the latter was also used to assess associations between proteinuria/eGFR (≥/< 60 mL/minute) and patient characteristics (gender, age), treatment, and urinary parameters.

Analysis of variance was performed using a linear model to investigate the statistical effects of gender, renal echogenicity, and TDF treatment on eGFR (mean ± standard error [SE]). The analysis was adjusted for covariates (age and CD4 count). Interactions between factors were examined.

Initial status data from the time of enrolment were compared with long-term follow-up data using paired tests (*t* test or Wilcoxon, depending on normality). The distribution of measurements was checked for normality using the Kolmogorov–Smirnov test. Results were considered significant at a P value ≤ 0.05 for 2-sided tests.

RESULTS

One hundred and seventy-nine patients were screened and enrolled in the study, 132 of them (73.7%) were on cART. One hundred and nineteen of the 132 patients on treatment (90.1%) had been on TDF-containing regimens over a mean period of 301 ± 193 days. Of the remaining 13 patients (9.9%), two patients were on abacavir-containing regimens because of suspected resistance problems. Eleven patients were on azidothymidine (AZT)-containing regimens, five of them due to renal insufficiency. The reason the other six were on AZT was not discernible. Because of the low number of patients not on TDF, only the 119 patients on TDF-containing regimens were compared with the treatment-naïve patients.

An analysis of the patient characteristics (Table 1) shows that patients on cART were significantly older and had significantly higher CD4 cell counts than their treatment-naïve counterparts.

Ninety-five patients presented with abnormal urinalysis results (57.2%), including 55 patients with proteinuria (35.4%), 54 with leukocyturia (32.9%), and 48 with erythrocyturia (29.3%) (Table 1). Only proteinuria was significantly more prevalent among treatment-naïve patients than those on treatment (52.2% versus 26.1%; $P = 0.003$), whereas the groups were similar with regard to leukocyturia and erythrocyturia.

Although serum creatinine was significantly higher in treatment-naïve patients ($P = 0.009$), the mean eGFR was comparable in the two groups ($P = 0.143$).

Forty-eight of 166 patients (28.9%) had an eGFR < 60 mL/minute, and the proportion of patients with an eGFR < 60 mL/minute was significantly higher among treatment-naive patients than those on TDF treatment (40.4% versus 24.4%; $P = 0.041$). Although the mean arterial blood pressure was significantly higher in treatment-experienced patients ($P = 0.002$), the proportion of patients diagnosed with arterial hypertension did not differ significantly between treatment-naïve patients and patients on TDF ($P = 0.053$).

The ultrasound study revealed the kidneys to be significantly larger in treatment-naïve patients than in patients on TDF ($P < 0.001$). However, renal echogenicity did not differ between the two groups.

Proteinuria was significantly associated with CD4 cell counts, antiretroviral treatment, eGFR, and renal echogenicity (Table 2). Age, gender, treatment duration, treatment regimen (protease inhibitors [PIs] or non-nukleoside transcriptase inhibitors), arterial hypertension, and the WHO stage of HIV infection had no significant influence on proteinuria. Of all these parameters, only renal echogenicity was found to associate significantly with eGFR (≥/< 60 mL/minute, $P = 0.002$; Table 2).

Multivariate analysis revealed renal echogenicity ($P < 0.001$), ARV treatment ($P = 0.038$), and age ($P < 0.001$) to influence eGFR measurements significantly (Table 3).

Sixteen patients were available for follow-up after a median time of 220 days (134–240). Mean CD4 cell counts had risen significantly from 259 to 412/μL, whereas median serum creatinine levels had fallen significantly, and the mean eGFR had risen from 68.4 to 78.7 mL/minute (Table 4). Eleven of the patients subjected to follow-up were on TDF-containing regimens, and five patients were on AZT-containing regimens. Those on AZT-containing regimens had displayed higher creatinine levels and lower eGFR values before starting treatment than those who started on TDF. The changes in creatinine levels and eGFR were only significant among those on AZT treatment (Table 4).

TABLE 1
Characteristics of study population

	All patients $N = 166$	TDF treatment $N = 119$	Treatment-naïve = 47	P value
Female, No. (%)	112 (67.5)	86 (72.3)	26 (55.3)	0.044
Age (years), median (Q1, Q3) (min.–max.)	42 (35, 49) (18–70)	44 (36, 50) (18–69)	37 (31, 46) (20–70)	0.006
Serum creatinine (mg/dL), median (Q1, Q3)	1.2 (1, 1.4)	1.1 (0.9, 1.3)	1.2 (1, 1.7)	0.009
eGFR (mL/min), mean (SD)	76.3 (26.8)	78.2 (26.0)	71.4 (29.6)	0.143
eGFR < 60/mL/min, No. (%)	48 (28.9)	29 (24.4)	19 (40.4)	0.041
Current CD4-count/μL mean (SD)	387 (259)	460 (255)	204 (158)	< 0.001
WHO status, No. (%)	162 (100)	116 (100)	46 (100)	0.007
I	39 (24.1)	21 (18.1)	18 (39.1)	
II	30 (18.5)	27 (23.2)	3 (6.5)	
III	76 (46.9)	54 (46.6)	22 (47.9)	
IV	17 (10.5)	14 (12.1)	3 (6.5)	
Proteinuria, No. (%)	55 (35.4)	31 (26.1)	24 (52.2)	0.003
Erythrocyturia (> 5/μL), No. (%)	48 (29.3)	32 (27.1)	16 (34.8)	0.310
Leukocyturia, No. (%)	54 (32.9)	41 (34.5)	13 (28.9)	0.578
Glucosuria, No. (%)	3 (1.8)	3 (2.5)	–	0.561
Renal echogenicity, No. (%)				0.376
Normal	105 (63.3)	73 (61.3)	32 (68.1)	
G1	54 (32.5)	42 (35.3)	12 (25.5)	
G2	7 (4.2)	4 (3.4)	2 (4.3)	
Kidney size (cm), mean (SD)	10.6 (1.1)	10.3 (1.0)	11.1 (1.2)	< 0.001
mean arterial blood pressure (mm of Hg), median (Q1, Q3)	91.7 (83.3, 100)	93.3 (84.6, 103)	86.7 (83.3, 93.3)	0.002
arterial hypertension (> 140/90), No. (%)	47 (29.6)	39 (34.2)	8 (17.8)	0.053
fasting blood sugar (mg/dL), median (Q1, Q3)	84 (73, 96)	84 (73, 94)	85 (69.5, 99.3)	0.955
TBC, No. (%)	8 (4.8)	1 (0.8)	7 (14.9)	0.001

eGFR = estimated glomerular filtration rate (by CKD EPI formula); TBC = tuberculosis. P value comparing patients on TDF treatment with treatment-naïve patients.

DISCUSSION

The proportion of treatment-naïve patients with abnormal urinalysis was 57.2% in our study. Proteinuria was present in 35.4% of all patients and in 52.2% of treatment-naïve patients. This rate of abnormal urinalysis is higher than that reported in a previous study from Cameroon, where the percentage of treatment-naive patients with abnormal urinalysis was 41% and the rate of proteinuria was 36%.[4] One possible reason for the high rate of proteinuria in our study may have been a high rate of urinary tract infections. The proportion of patients displaying proteinuria without leukocyturia was 20.5% and was significantly higher among treatment-naïve patients than those on TDF treatment (34.04% versus 15.1%, Table 2, P = 0.003). Only a few studies to date have assessed proteinuria in Sub-Saharan Africa. In Nigeria, the prevalence of proteinuria among treatment-naïve patients was, at 36%,[22] similar to that found in our study. However, this contrasts studies from Kenya, Rwanda, and South Africa, where the prevalence of proteinuria did not exceed 10%.[24,28,29]

In our cohort, the prevalence of chronic kidney disease, defined as eGFR < 60 mL/minute (Stage 3 and worse), was 28.9% (40.4% among treatment-naïve patients versus 24.4% among treatment-experienced patients) indicating a high rate of patients with renal dysfunction. This ties in with the results of other studies from Sub-Saharan Africa, which have found the rate of patients with eGFR < 60 mL/minute to range between 7% and 53%.[2,24,29–33] However, differences in the way in which eGFR was calculated makes a direct comparison between the studies difficult. In our study, CKD-EPI was used because recent data suggest that this method of GFR estimation has the highest level of accuracy in HIV-infected adults.[5]

In Cameroon, TDF has formed a part of the first-line treatment of HIV patients since 2014. Although TDF is generally considered to be safe and well-tolerated, it has been linked to serious renal damage.[20,32,34] As a result, renal parameters need to be screened regularly during treatment. In many Sub-Saharan African countries, however, this screening is not performed systematically, and to the best of our knowledge, no data on TDF use and renal impairment in HIV patients in Cameroon has been available until now.

In our cohort, patients on TDF had lower creatinine values, higher eGFR values, and a lower prevalence of abnormal dipstick results than treatment-naive patients. This suggests that cART is beneficial to renal function. cART has been found to be associated with a decrease in HIV-associated renal dysfunction and in progression to end-stage renal disease worldwide.[1,32,34,35] However, when TDF was not part of the treatment regimens, a study from Ghana found the prevalence of patients with an eGFR < 60 mL/minute to be higher among those on cART than among treatment-naïve patients.[36]

In the study presented here, low CD4 cell counts are associated with an increased risk of proteinuria, as well as with cART. This echoes other studies that describe an improvement in renal function under antiretroviral treatment.[1,32,34,35] Although PIs, especially atazanavir, have been described as potentially nephrotoxic,[11,37] no significant association between PI use and proteinuria or PI use and a decreased eGFR were detectable in our study. However, the number of patients on PIs was small.

Arterial hypertension and diabetes mellitus are independent risk factors for chronic kidney disease.[11,38,39] In our cohort, diabetes was not prevalent and fasting blood sugar levels were similar in treatment-experienced and treatment-naive patients. Arterial hypertension was more prevalent in

TABLE 2
Proteinuria and eGFR with associated parameters

	Proteinuria			eGFR		
	Negative	Positive	*P* value	≥ 60 (mL/min)	< 60 (mL/min)	*P* value
n (%)	110	55		119	47	
Female	80 (72.7)	32 (58.2)	0.077	78 (65.5)	34 (72.3)	0.464
Age, years			0.474			0.069
18–35	30 (27.3)	18 (32.7)		40 (33.6)	8 (17.0)	
36–55	63 (57.3)	32 (58.2)		66 (55.5)	30 (63.8)	
> 55	17 (15.5)	5 (9.1)		13 (10.9)	9 (19.1)	
CD4-count			< 0.001			0.237
≥ 500/μL	46 (41.8)	5 (9.1)		41 (34.5)	10 (21.3)	
200–499/μL	49 (44.5)	22 (40.0)		48 (40.3)	24 (51.1)	
< 200/μ	15 (13.6)	28 (50.9)		30 (25.2)	13 (27.7)	
Renal echogenicity			0.047			0.002
Normal	75 (68.2)	30 (54.5)		85 (71.4)	20 (42.6)	
G1	33 (30.0)	20 (36.4)		31 (26.1)	23 (48.9)	
G2	2 (1.8)	5 (9.1)		3 (2.5)	4 (8.5)	
WHO-status	*N* = 108 (100%)	*N* = 53 (100%)	0.504	*N* = 117 (100%)	*N* = 45 (100%)	0.593
I	24 (22.2)	15 (28.3)		28 (23.9)	11 (24.4)	
II	23 (21.3)	7 (13.2)		23 (19.7)	7 (15.6)	
III	51 (47.2)	24 (45.3)		56 (47.9)	20 (44.4)	
IV	10 (9.3)	7 (13.2)		10 (8.5)	7 (15.6)	
Treatment			0.003			0.086
Yes	88 (80.0)	31 (56.4)		90 (75.6)	29 (61.7)	
No	22 (20.0)	24 (43.6)		29 (24.4)	18 (38.3)	
Treatment	*N* = 88 (100%)	*N* = 31 (100%)	1.000	*N* = 90 (100%)	*N* = 29 (100%)	0.516
PI	10 (11.4)	3 (9.7)		9 (10.0)	4 (13.8)	
NNRTI	78 (88.6)	28 (90.3)		81 (90.0)	25 (86.2)	
Treatment duration	*N* = 88 (100%)	*N* = 31 (100%)	0.142	*N* = 90 (100%)	*N* = 29 (100%)	1.000
< 5 years	34 (38.6)	17 (54.8)		39 (43.3)	12 (41.4)	
≥ 5 years	54 (61.4)	14 (45.2)		51 (56.7)	17 (58.6)	
Art. HPT	*N* = 107 (100%)	*N* = 51 (100%)	0.713	–	–	0.345
Yes	33 (30.8)	14 (27.5)		36 (31.9)	11 (23.9)	
No	74 (69.2)	37 (72.5)		77 (68.1)	35 (76.1)	
eGFR			0.010	–	–	–
≥ 60 mL/min	86 (78.2)	32 (58.2)				
< 60 mL/min	24 (21.8)	23 (41.8)				

eGFR = estimated glomerular filtration rate (CKD EPI); HPT = hypertension; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor. *P* values obtained by Pearson's χ^2 test for independence and Fisher's exact test (2 × 2 tables), respectively.

treatment-experienced patients, but was not found to be significantly associated with either proteinuria or eGFR. The higher prevalence of arterial hypertension among treatment-experienced patients than treatment-naive patients might be explained by the age difference between the two groups because the prevalence of hypertension increases with age.[40]

In a multivariate analysis, eGFR was shown to be independently associated with cART, renal echogenicity, and age, but not with CD4 cell counts. cART has been observed to have a beneficial effect on renal function in other studies from Sub-Saharan Africa,[31,32] a finding which ties in with the fact that HIV-associated renal dysfunction has decreased since the introduction of cART.[1,35]

In our cohort, treatment with TDF was not associated with an increase in serum creatinine or a decrease in eGFR after 6 months of therapy. This echoes other studies in which TDF is described as being well-tolerated with a low incidence of renal side effects.[6,7] Studies from Nigeria and Senegal, on the other

TABLE 3
Multiple variance analysis for eGFR

Factor	eGFR (mL/min) Mean ± SE (95% CI) adjusted for age and CD4	Effect caused proportion of eGFR variance	*P* value
	64.2 ± 3.8 (56.5–71.7)	–	–
Renal echogenicity		11%	< 0.001
Normal*	81.9 ± 2.8 (76.3–87.4)		0.009
G1	66.0 ± 4.5 (57.1–75.0)		0.001
G2	44.6 ± 10.1 (24.6–64.6)		
cART		3%	0.038
No*	55.9 ± 6.0 (44.0–67.8)		
Yes	72.5 ± 5.0 (62.6–82.3)		
Gender		< 1%	0.591
Female*	62.1 ± 5.3 (51.5–72.6)		
Male	66.2 ± 5.6 (55.2–77.3)		
Age (years)	–	11%	< 0.001
CD4 cells (count/μL)	–	< 1%	0.255

cART = combined antiretroviral treatment; eGFR = estimated glomerular filtration rate (CKD EPI). No significant factor interactions could be detected.

TABLE 4
Development of creatinine, eGFR, and proteinuria after start of ARV treatment

	All (N = 16)			TDF (N = 11)			AZT (N = 5)		
Age (years), median (Q1, Q3) (min.–max.)	37 (29, 47) (21–55)			34 (28, 46) (21–55)			46 (38, 48) (36–48)		
Duration of treatment (days), median (Q1, Q3) (min.–max.)	– 220 (212, 231) (134–240)			– 219 (209, 232) (134–240)			– 222 (216, 232) (212–235)		
	Before	After	P	Before	After	P	Before	After	P
CD4-count/μL, mean (SD)	259 (159)	412 (177)	0.004	263 (166)	410 (187)	0.019	252 (163)	416 (170)	0.159
Creatinine (mg/dL), median (Q1, Q3)	1.4 (1.0, 1.7)	1.2 (1.1, 1.3)	0.023	1.2 (1.0, 1.5)	1.2 (1.0, 1.3)	0.426	1.7 (1.7, 2.3)	1.2 (1.2, 1.2)	0.043
eGFR (mL/min), mean (SD)	68.4 (25.2)	78.7 (18.3)	0.060	79.0 (22.4)	80.83 (20.6)	0.730	45.1 (11.7)	74.0 (12.3)	0.009
Proteinuria, n	5	5	–	1	3	–	4	2	–

AZT = azidothymidine; eGFR = estimated glomerular filtration rate; TDF = tenovofir-diproxil fumarate.

hand, have pointed to a decline in GFR under TDF treatment, compared with a stable or even rising GFR in the TDF-free arm.[10,19] The number of patients involved in these studies was higher and the duration of treatment longer than in the study presented here. In our study, five treatment-naïve patients with very low eGFR and high serum creatinine levels were started on regimens containing AZT instead of TDF. In Cameroon, TDF is only available as a combination tablet with lamivudine, making a dose adjustment for patients with a low eGFR impossible. Nevertheless, all 16 patients, including those on TDF-containing regimens, benefited from cART, as shown by decreased creatinine levels and increased CD4 cell counts.

One limitation of the study presented here is the unequal distribution of both age and gender, which occurs frequently in cross-sectional studies and leads to unbalanced groups. In addition, the number of patients newly diagnosed with HIV was lower than the number of patients already on treatment at the time of enrolment. However, the inclusion of age and gender as independent variables in the multivariate analysis did not change the results. Because laboratory testing was carried out in the local laboratory to support local facilities and simulate real-life conditions, we were not able to measure beta-microglobuline in urine samples to detect specifically TDF-associated nephropathies or Hepatitis C prevalence in our cohort. Hepatitis C virus infection is associated with an increased risk of chronic kidney disease.[5,41,42] Despite our best efforts, it was not possible to mobilize a higher number of patients for follow-up.

In conclusion, this is the first study, to the best of our knowledge, to investigate the impact of TDF on renal parameters in Cameroon. TDF seems to be safe and does not appear to be a significant cause of renal impairment. However, renal parameters should still be monitored regularly, as recommended by the guidelines, to permit early identification of a rise in serum creatinine levels or a decline in the eGFR, and allow the substitution of an alternative antiretroviral agent for TDF as appropriate. In future, the introduction of the less nephrotoxic tenofovir alafenamide in Sub-Saharan Africa will probably make the management of nephrotoxic side effects easier.

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