Association Between Tenofovir Exposure and Reduced Kidney Function in a Cohort of HIV-Positive Patients: Results From 10 Years of Follow-up

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Background. Some studies have shown that tenofovir disoproxil fumarate (TDF), a drug widely used in highly active antiretroviral therapy, is associated with kidney dysfunction, but the magnitude of the effect and its clinical impact is still being debated. Our objective was to evaluate the association between long-term TDF exposure and kidney dysfunction in a cohort of 1043 human immunodeficiency virus–positive patients followed up for 10 years and to quantify the loss in estimated glomerular filtration rate (eGFR) in patients exposed to TDF in comparison with those exposed to other antiretroviral therapies.

Methods. Adjusted hazard ratios (HR) and odds ratios (OR) for the association between TDF and kidney dysfunction (defined as eGFR <90 mL/min/1.73 m^2) were calculated using the Cox proportional hazards model and generalized estimating equations. Mean loss in eGFR attributable to TDF by cumulative years of exposure was estimated using linear regressions.

Results. Tenofovir exposure increased the risk of kidney dysfunction by 63% (HR, 1.63; 95% confidence interval, 1.26–2.10). The cumulative eGFR loss directly attributable to TDF after 1, 2, 3, and 4 years of TDF exposure was −3.05 ($P = .017$), −4.05 ($P = .000$), −2.42 ($P = .023$), and −3.09 mL/min/1.73 m^2 ($P = .119$), respectively, which shows that most of the loss occurred during the first years of exposure.

Conclusions. In this cohort, TDF exposure was associated with reduced kidney function, but the loss in eGFR attributable to TDF is relatively mild in a long-term perspective.

Keywords. HIV; antiretroviral therapy; estimated glomerular filtration rate; kidney function; tenofovir.

Kidney dysfunction is associated with morbidity and mortality in human immunodeficiency virus (HIV)–positive patients and clinical follow-up is therefore important [1]. HIV infection itself has been identified as a risk factor for kidney dysfunction [2], as have many other non–HIV-related factors, such as baseline glomerular filtration rate <90 or <60 mL/min/1.73 m^2, high HIV load, low CD4 cell count, female sex, older age, black race, low weight and comorbid conditions (diabetes, hepatitis B or C, hypertension, proteinuria, albuminuria) [3–7]. Atazanavir, didanosine, indinavir, lopinavir/ritonavir, other nephrotoxic drugs, and recreational drugs, particularly cocaine, have also been identified as risk factors for loss of kidney function [6, 8–12]. Many studies have shown that tenofovir disoproxil fumarate (TDF), a drug widely used in highly active antiretroviral therapy (ART) is associated with kidney dysfunction, but the magnitude of the effect and its clinical impact are still being debated [13, 14]. Discrepancies in the literature

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can be explained by lack of power or limited sample size, dissimilar study populations, short follow-up, and different analysis strategies.

In an effort to inform the current debate, our objective was to evaluate the association between long-term TDF exposure and kidney dysfunction and to quantify the loss in estimated glomerular filtration rate (eGFR) attributable to TDF in a cohort of HIV-positive patients exposed to ART and followed up between January 2002 and March 2012.

METHODS

Patients and Data Collection

We used data from an open cohort of 2352 HIV-infected patients at the Clinique Médicale du Quartier Latin in Montreal, Canada. The cohort started in July 1997; recruitment and follow-up are still ongoing. All participants signed an informed-consent form at enrollment, the first appointment related to their HIV diagnosis. The study protocol was approved by the research ethics committee of Sainte-Justine Hospital. Data collected include sociodemographic information, a complete history of ARTs and results of laboratory tests, such as CD4 cell count, HIV-RNA viral load and serum creatinine level, which have generally been done every 3 months since 1997. All clinical data were collected prospectively, although certain sociodemographic data, such as race, socioeconomic status, and sexual orientation, were gathered retrospectively.

Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for every visit for which a serum creatinine test was available. CKD-EPI is recommended for routine clinical use in HIV-positive patients instead of the modification of diet in renal disease (MDRD) equation, which may overestimate the severity of renal impairment in HIV-positive patients [15–17], because it is known to be more accurate at high glomerular filtration rates and as good at low rates.

Statistical Analysis

Because TDF was approved by the US Food and Drug Administration in October 2001, follow-up of exposed as well as unexposed patients were considered from 1 January 2002 to 7 March 2012. In other words, all patients became at risk on 1 January 2002 if they were exposed to any antiretroviral (ARV). All patients not exposed to ARVs or not entered in the cohort at that date entered in the analysis (became at risk) in the course of follow-up at the time they became exposed to any ARVs. Patients who had taken TDF alone or in combination were considered to be exposed to TDF. Patients exposed to any ARV except TDF were considered to be unexposed.

The classification of stages of chronic kidney disease in the National Kidney Foundation's Practice Guidelines for Chronic Kidney Disease was used to establish a cut point for decreased kidney function, eGFR <90 mL/min/1.73 m^2[18]. Kaplan-Meier analysis was used to estimate the cumulative incidence of reduced kidney function according to exposure status. Failure (outcome) was considered to occur only after 2 consecutive measurements of eGFR <90 mL/min/1.73 m^2 ≥3 months apart. Patients were followed up until failure occurred or, for censored observations, until the most recent recorded visit for which an eGFR measurement was available. We used the log-rank test to assess the significance of differences in incidence of reduced kidney function by exposure status.

We used 2 types of regression models to analyze the association between TDF exposure and kidney function. First, we used Cox proportional hazards regression modeling to calculate hazard ratios (HR) and respective 95% confidence intervals (CIs) for the association between reduced kidney function (2 consecutive measurements of eGFR <90 mL/min/1.73 m^2 ≥3 months apart) and ARV exposure (TDF vs other ARVs). As Cox regression models incidence data, patients with eGFR <90 mL/min/1.73 m^2 at baseline (prevalent cases) were excluded. Patients exposed to TDF for <3 months were also excluded. Multivariate model was built to control a priori for confounders and included the following variables measured at baseline: eGFR, age, sex, race, sexual orientation, monthly income, type of employment, smoking, and injection drug users (IDUs); it also included the following time-dependent variables: alcohol consumption, diabetes, hypertension, HIV-RNA viral load CD4 cell count, and use of nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors, or HIV integrase strand transfer inhibitors (INSTIs). Possible interactions of age, diabetes, hypertension, and use of PIs on the association of TDF and eGFR were verified.

We also performed generalized estimating equation (GEE) logistic regression, which essentially correlates outcome and exposure cross-sectionally by taking into account the clustering within each individual caused by the repeated-measurements design. Cox modeling does not allow to analyze what happens after failure, whereas GEE analysis can handle repeated events within a subject. GEE analysis was therefore used as a secondary analysis to document the complete trajectory of patients with multiple repeated events and to confirm the role of TDF in kidney function. The models incorporated an exchangeable correlation pattern for repeated events. Outcome was defined as eGFR <90 mL/min/1.73 m^2, and exposure status as exposure to TDF versus exposure to any other ARVs. The multivariate model was built to control a priori for confounders and included the following variables measured at baseline: eGFR, sex, race, sexual orientation, monthly income, type of employment, smoking, and injection drug use; it also included time-varying variables: tenofovir exposure, age, alcohol consumption,

diabetes, hypertension, HIV-RNA viral load, CD4 cell count, and use of NRTIs, NNRTIs, fusion inhibitors, entry inhibitors, INSTIs, and PIs.

To further study the impact of TDF on kidney function, we calculated the mean loss in eGFR per year after exposure to TDF compared with other ARVs. Loss per cumulative year of exposure (measured from the beginning of exposure) was calculated for every patient, along with a mean loss in eGFR per cumulative year. Linear regression was used to estimate the cumulative loss in eGFR per year directly attributable to TDF exposure. A multivariate linear regression model was used to control for empirical confounders, using the 5% change in estimates method. All analyses were done using Stata/SE 11 (StataCorp).

RESULTS

Of 2352 patients, 2058 were followed up after January 2002, 630 were excluded because they were not actively followed up at the clinic (had not been seen at least once in the last 2 years), 242 were excluded because they had no eGFR measurements or missing information about race, which is required for the calculation of CKD-EPI, and 143 were excluded because they were not exposed to any ARVs. The baseline characteristics of the 1043 patients included in the analysis are shown in Table 1. The median length of follow-up was 7.9 years. The median age at baseline was 39.3 years, and 3.8% of the cohort were women. The median number of eGFR measurements (per patient) for the TDF-exposed group was 19 (interquartile range [IQR], 10–30) and 25 (IQR, 15–34) for the unexposed group. The median time between serum creatinine measurements was 97 days (IQR, 84–125 days) for the exposed group and 98 days (IQR, 84–120 days) for the unexposed group. The group exposed to TDF differed from the unexposed group (exposed to other ARVs) in terms of monthly income: 20.4% of those exposed have a monthly income <$1500, in contrast to 14.7% of those not exposed. The HIV-RNA viral load at baseline was lower in the unexposed group than in the exposed group (median, 467 and 2198 HIV RNA copies/mL, respectively), and IDUs were more frequent in the unexposed group (41.2% vs 33.6%)

Association Between Tenofovir and Reduced Kidney Function

Figure 1 shows the cumulative incidence of reduced kidney function (defined as 2 consecutive measurements of eGFR <90 mL/min/1.73 m^2 ≥3 months apart), over a 10-year period, by exposure status. The cumulative incidence of reduced kidney function after 2, 5, and 10 years of exposure to TDF was 15.12% (95% CI, 11.15–20.34), 31.47% (95% CI, 26.17–37.54), and 52.29% (95% CI, 45.65–59.26), respectively. In the unexposed group, the cumulative incidence after 2, 5, and 10 years was 10.27% (95% CI, 7.94–13.23), 25.89% (95% CI, 21.78–30.62), and 40.53% (95% CI, 34.82–46.80), respectively. The log-rank test showed that the difference is statistically significant ($P = .024$).

In total, there were 271 incident cases of reduced kidney function for 4285.00 person-years (incidence rate [IR], 63.2 per 1000 person-years; 95% CI, 56.2–71.2). In the TDF-exposed group, 133 events occurred for 1809.66 person-years (IR, 73.5 per 1000 person-years; 95% CI, 62.0–87.1) and for the unexposed group, 138 events occurred for 2475.34 person-years (IR, 55.8 per 1000 person-years; 95% CI, 47.2–65.9).

Table 2 shows the results for the Cox proportional hazards regression model. Tenofovir exposure increased the risk of reduced kidney function by 63% (adjusted HR, 1.63; $P = .000$) compared with other ARV exposure. Other determinants associated with a significant increased risk were older age at baseline (HR, 1.03; $P = .004$; every additional year of age increased the risk by 3%), lower eGFR at baseline (HR, 0.93; $P = .000$; every additional mL/min/1.73 m^2 of eGFR at baseline decreased the risk by 7%), and alcoholic status (HR, 2.04; $P = .022$). NRTI users (HR, 0.39; $P = .019$) had a lower risk than nonusers of NRTIs, and PI users (HR, 1.46; $P = .018$) had a higher risk than nonusers of PIs. The relation between TDF and kidney function was not affected by interaction with age, use of PIs, diabetes, or hypertension (data not shown).

Table 3 reports the results for the GEE logistic regression models. Exposure to TDF increased the risk of reduced kidney function by 63% (odds ratio [OR], 1.63; $P = .000$). Other determinants that increased the risk significantly were older age (OR, 1.06; $P = .000$; 6% greater risk for each additional year of age), lower eGFR at baseline (OR, 0.93; $P = .000$), alcoholic status (OR, 1.57; $P = .020$), INSTI use (OR, 1.49; $P = .000$), and PI use (OR, 1.82; $P = .000$). Finally, black patients had a lower risk than patients of other races (OR, 0.39; $P = .019$), and smokers had a lower risk than patients who had never smoked (OR, 0.73; $P = .000$).

Quantification of Mean Loss in eGFR

Table 4 quantifies mean loss in eGFR by exposure status. Cumulative mean loss in eGFR was calculated after 1, 2, 3, 4, 5, and ≥6 years of exposure to TDF or any other ARVs. For the group exposed to TDF, cumulative mean loss increased consistently over the years, from −3.31 mL/min/1.73 m^2 after 1 year of exposure to −10.46 mL/min/1.73 m^2 after ≥6 years. For the unexposed group, cumulative mean loss in eGFR started at −0.25 mL/min/1.73 m^2 after 1 year of exposure and reached −9.42 mL/min/1.73 m^2 after ≥6 years. The univariate models show the cumulative mean loss directly attributable to TDF exposure. The multivariate models show that the adjusted mean loss directly attributable to TDF exposure after 1 year of exposure was −3.05 mL/min/1.73 m^2. However, there was

Table 1. Baseline Characteristics of 1043 HIV-Infected Patients by Tenofovir Disoproxil Fumarate Exposure Status at End of Follow-up

Characteristic	No. (%) or Median (IQR)[a]		
	Exposed to TDF	Unexposed to TDF (Exposed to Other ARVs)	All
All	736 (70.6)	307 (29.4)	1043 (100)
Sex			
Male	706 (95.9)	297 (96.7)	1003 (96.2)
Female	30 (4.1)	10 (3.3)	40 (3.8)
Race			
White	679 (92.3)	279 (90.9)	958 (91.9)
Black	17 (2.3)	12 (3.9)	29 (2.8)
Other	40 (5.4)	16 (5.2)	56 (5.4)
Diabetes			
Yes	27 (3.7)	19 (6.2)	46 (4.4)
No	681 (92.5)	275 (89.6)	956 (91.7)
Hypertension			
Yes	103 (14.0)	60 (19.5)	163 (15.6)
No	605 (82.2)	234 (76.2)	839 (80.4)
Smoking			
Never smoked	257 (34.9)	104 (33.9)	361 (34.6)
Smoker	212 (28.8)	84 (27.4)	296 (28.4)
Former smoker	180 (24.5)	87 (28.3)	267 (25.6)
Alcohol consumption			
None	75 (10.2)	31 (10.1)	106 (10.2)
Former drinker	33 (4.5)	14 (4.6)	47 (4.5)
Social drinker	516 (70.1)	221 (72.0)	737 (70.7)
Alcoholic	57 (7.8)	24 (7.8)	81 (7.8)
Injection drug user			
Yes	247 (33.6)	126 (41.2)	373 (35.8)
No	273 (37.1)	115 (37.5)	388 (37.2)
Country of birth			
Canada	643 (87.4)	272 (88.6)	915 (87.8)
Other	88 (12.0)	32 (10.4)	120 (11.5)
Sexual orientation			
Homosexual	625 (84.9)	263 (85.7)	888 (85.1)
Heterosexual	69 (9.4)	26 (8.5)	95 (9.1)
Other	28 (3.8)	11 (3.6)	40 (3.8)
Monthly income			
≤$1500	150 (20.4)	45 (14.7)	195 (18.7)
>$1500	523 (71.2)	237 (77.2)	760 (72.9)
Unknown	3 (0.4)	1 (0.3)	4 (0.4)
Employment			
Full time	348 (47.3)	152 (49.5)	404 (38.7)
Other	284 (38.6)	120 (39.1)	500 (47.9)
Continuous variables			
Age, y	39.0 (33.9–44.8)	40.2 (34.5–46.2)	39.3 (34.0–45.2)
Duration of HIV infection, y	6.54 (3.01–12.01)	6.47 (2.89–12.25)	6.50 (2.99–12.04)
Follow-up duration, y	7.2 (3.0–9.5)	8.6 (4.8–9.6)	7.9 (3.4–9.6)
Viral load, HIV RNA copies/mL	2,198 (49–46,887)	467 (49–37,040)	1550 (49–42 285)

Table 1 continued.

Characteristic	No. (%) or Median (IQR)[a]		
	Exposed to TDF	Unexposed to TDF (Exposed to Other ARVs)	All
CD4 cell count, cells/mm^3	460 (300–673)	480 (320–840)	471 (310–680)
eGFR, mL/min/1.73 m^2	104.9 (94.2–113.1)	103.5 (93.4–112.2)	104.5 (93.8–112.9)

Baseline characteristics were determined at first HIV-related appointment on or after 1 January 2002. Diabetes and hypertension status were defined according to the diagnosis or related medication, and data represent the period prevalence. Missing data are not listed, and total frequencies may differ slightly from total numbers of patients.

Abbreviations: ARV, antiretroviral; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, interquartile range; TDF, tenofovir disoproxil fumarate.

[a] Data represent medians (IQRs) for continuous variables and No. (%) of patients for all other characteristics.

no clear trend associated with the number of years of exposure; the adjusted cumulative mean loss were relatively stable over the years (−3.05, −4.05, −2.42, and −3.09 mL/min/1.73 m^2 after 1, 2, 3, and 4 years of exposure, respectively) indicating that most of the loss was acquired during the first year of exposure and stabilized after that.

DISCUSSION

In this study, we evaluated the association between TDF exposure and kidney function and quantified the mean loss in eGFR attributable to TDF through the cumulative years of exposure. The Kaplan-Meier curve shows that the cumulative incidence of reduced kidney function is higher among patients exposed to TDF than among those exposed to other ARVs ($P = .024$). We used 2 different regression models (GEE and Cox modeling) and found that there was a consistently higher risk of reduced kidney function associated with exposure to TDF than with any other ARVs. Cox modeling analysis showed that TDF exposure increased the risk of reduced kidney function by 63% (adjusted HR, 1.63; 95% CI, 1.26–2.10). Other researchers have made comparable findings. For example, in a large cohort of 10 841 HIV-infected patients with a median follow-up of 3.9 years, Scherzer et al [11] used a similar strategy with Cox modeling, although the outcome was defined by an eGFR <60 mL/min/1.73 m^2. They found a 33% higher risk of chronic kidney disease, defined as 2 consecutive measurements of eGFR <60 mL/min/1.73 m^2 ≥3 months apart, calculated with the MDRD formula. They also found that 11% of patients newly exposed to TDF had a rapid annual decline in eGFR (defined as a loss of ≥3 mL/min/1.73 m^2 in 2 consecutive years).

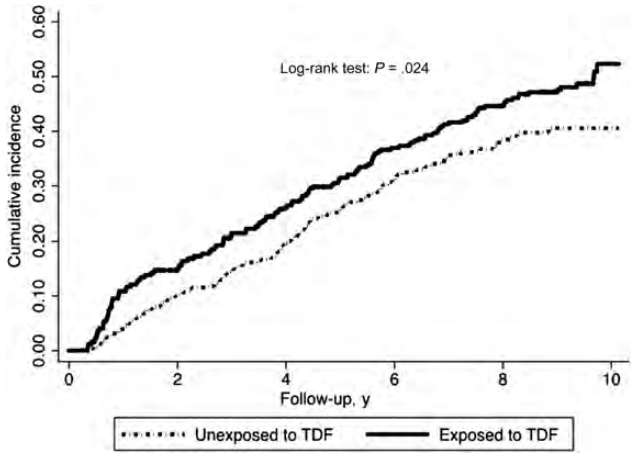

Figure 1. Kaplan-Meier graph of cumulative incidence of reduced kidney function, stratified by antiretroviral exposure. Outcome defined as 2 consecutive estimated glomerular filtration rate measurements <90 mL/min/1.73 m^2 ≥3 months apart. Abbreviation: TDF, tenofovir disoproxil fumarate.

We also analyzed determinants of renal function with GEE modeling, which allows multiple events (persistent kidney dysfunction) to be taken into account. We confirmed that TDF exposure increases the risk of renal dysfunction (adjusted OR, 1.63; 95% CI, 1.48–1.79). We observed no effect modification (interaction) for age, PI use, diabetes or hypertension in the association between TDF and renal function. For example, older patients (aged ≥50 years) exposed to TDF were at no greater risk of kidney dysfunction than those <50 years old.

We also found that adjusted loss in eGFR directly attributable to TDF exposure was −3.05 mL/min/1.73 m^2 after 1 year of treatment. In a systematic review of 17 studies (including 9 randomized controlled trials), Cooper et al [13] found that the pooled loss attributable to TDF was −3.72 mL/min/1.73 m^2.

Importantly, we found that adjusted loss in eGFR directly attributable to TDF exposure was −3.05 mL/min/1.73 m^2 after 1 year of treatment and that this loss stayed relatively constant through the following years of exposure. Losses were −4.05 ($P = .000$), −2.42 ($P = .023$), −3.09 ($P = .119$), −0.12 ($P = .946$), and 0.32 mL/min/1.73 m^2 ($P = .898$) after 2, 3, 4, 5, and

Table 2. Determinants of Reduced Kidney Function: Univariate and Multivariate Analysis Using Time-Dependent Cox Model

	Univariate		Multivariate	
Variables[a]	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
TDF exposure, yes vs no	1.33 (1.04–1.69)	.024	1.63 (1.26–2.10)	.000
eGFR at baseline, mL/min/1.73 m^2 (continuous)[b]	0.92 (.91–.93)	.000	0.93 (.91–.94)	.000
Age at baseline, y (continuous)	1.07 (1.05–1.08)	.000	1.03 (1.01–1.05)	.004
Sex, female vs male	0.86 (.43–1.75)	.683	1.59 (.63–3.71)	.305
Race, black vs other	0.36 (.12–1.13)	.079	0.74 (.21–2.54)	.630
Sexual orientation, heterosexual vs homosexual	0.78 (.50–1.22)	.277	0.79 (.44–1.40)	.413
Monthly income, >$1500 vs ≤$1500	1.09 (.82–1.45)	.559	1.08 (.76–1.55)	.663
Employment, full time vs other	0.72 (.55–.93)	.014	0.88 (.64–1.22)	.438
Alcohol consumption				
None (reference)	1.00			
Former drinker	1.18 (.60–2.33)	.627	1.42 (.71–2.87)	.322
Social drinker	1.44 (.90–2.30)	.131	1.39 (.85–2.29)	.193
Alcoholic	1.79 (1.00–3.21)	.050	2.04 (1.11–3.73)	.022
Smoking, smoker or former smoker vs never smoked	0.87 (.67–1.13)	.290	0.76 (.57–1.00)	.053
Injection drug users, no vs yes	1.11 (.83–1.47)	.482	1.04 (.77–1.41)	.792
Hypertension, yes vs no	1.17 (.82–1.67)	.388	0.80 (.53–1.20)	.280
Diabetes, yes vs no	1.03 (.51–2.08)	.482	1.31 (.79–2.19)	.301
Viral load, HIV RNA copies/mL[c]				
0–400 (reference)	1.00		1.00	
401–10 000	0.42 (.22–.83)	.012	0.46 (.23–.91)	.026
10 001–99 999	0.47 (.19–1.13)	.093	0.54 (.22–1.37)	.196
≥100 000	3.84 (.54–27.56)	.180	2.86 (.36–22.94)	.323
CD4 cell count, cells/mm^3[d]				
0–200 (reference)	1.00		1.00	
200–499	1.39 (.80–2.43)	.241	1.22 (.67–2.23)	.512
≥500	1.22 (.70–2.12)	.484	1.09 (.60–2.01)	.776
NRTIs, yes vs no	0.38 (.18–.81)	.012	0.39 (.18–.86)	.019
NNRTIs, yes vs no	0.78 (.59–1.02)	.070	0.97 (.69–1.37)	.877
FIs, yes vs no	1.36 (.34–5.49)	.665	0.64 (.15–2.77)	.553
EIs, yes vs no	0.91 (.13–6.49)	.925	0.57 (.07–4.57)	.597
INSTIs, yes vs no	0.89 (.44–1.82)	.751	0.68 (.32–1.45)	.320
PIs, yes vs no	1.41 (1.10–1.82)	.007	1.46 (1.07–2.01)	.018

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EIs, entry inhibitors (maraviroc); FIs, fusion inhibitors (enfuvirtide); HIV, human immunodeficiency virus; HR, hazard ratio; INSTIs, HIV integrase strand transfer inhibitors (raltegravir); NNRTIs, nonnucleoside reverse-transcriptase inhibitors (efavirenz, etravirine, delavirdine, nevirapine, rilpivirine); NRTIs, nucleoside reverse-transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, zidovudine); PIs, protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir); TDF, tenofovir disoproxil fumarate.

[a] Variables measured at baseline: eGFR, age, sex, race, sexual orientation, monthly income, type of employment, smoking, and injection drug use; time-dependent variables: TDF exposure, alcohol consumption, diabetes, hypertension, viral load, CD4 cell count, and use of NRTIs, NNRTIs, PIs, FIs, EIs, and INSTIs. Of 1043 patients, 198 were excluded because they had an eGFR <90 mL/min/1.73 m^2 at baseline, 24 were excluded because they were exposed to TDF for <3 months, and 15 were excluded because they had failure at the first visit; 806 patients were included. Outcome was defined as 2 consecutive measurements of eGFR <90 mL/min/1.73 m^2 ≥3 months apart.

[b] Baseline defined as first appointment for an HIV-related condition on or after 1 January 2002 and exposure to any antiretroviral at the same time.

[c] Categorization based on clinical significance.

[d] Categorization based on World Health Organization guidelines.

≥6 years of exposure, respectively. This seems to indicate that the loss induced by TDF occurred mainly during the first year of exposure and stayed relatively constant afterward. Although comparison has to be made with caution as the CIs overlap, it is also possible that a few losses occurring during the first 2 years of exposure to TDF were recovered in the following

Table 3. Determinants of Prevalence of Reduced Renal Function: Univariate and Multivariate Analysis Using Generalized Estimating Equation Models

	Univariate Analysis		Multivariate Analysis[a]	
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
TDF exposure, yes vs no	1.84 (1.73–1.96)	.000	1.63 (1.48–1.79)	.000
eGFR at baseline, mL/min/1.73 m^2 (continuous)	0.92 (.91–.92)	.000	0.93 (.92–.93)	.000
Age, y (continuous)	1.11 (1.10–1.12)	.000	1.06 (1.05–1.07)	.000
Sex, female vs male	0.86 (.51–1.47)	.590	1.50 (.88–2.54)	.140
Race, black vs other	0.28 (.11–.67)	.004	0.39 (.18–.86)	.019
Sexual orientation, heterosexual vs homosexual	0.70 (.48–1.01)	.054	0.84 (.58–1.21)	.347
Monthly income, >$1500 vs ≤$1500	0.92 (.71–1.19)	.503	1.04 (.82–1.33)	.728
Employment, full time vs other	0.65 (.52–.80)	.000	0.90 (.73–1.10)	.301
Smoking, former smoker or smoker vs never smoked	0.74 (.60–.91)	.005	0.73 (.62–.87)	.000
Alcohol consumption				
None (reference)	1.00		1.00	
Former drinker	0.62 (.34–1.13)	.116	0.93 (.60–1.51)	.830
Social drinker	1.01 (.73–1.41)	.933	1.17 (.88–1.55)	.293
Alcoholic	1.16 (.73–1.85)	.532	1.57 (1.07–2.28)	.020
Injection drug user, no vs yes	1.32 (1.05–1.67)	.017	1.09 (.91–1.31)	.359
Diabetes, yes vs no	1.17 (.96–1.43)	.118	0.93 (.73–1.20)	.577
Hypertension, yes vs no	1.56 (1.40–1.73)	.000	1.06 (.91–1.23)	.473
Viral load, HIV RNA copies/mL[b]				
0–400 (reference)	1.00		1.00	
401–10 000	0.62 (.56–.70)	.000	0.85 (.81–1.01)	.062
10 001–99 999	0.71 (.60–.83)	.000	0.86 (.66–1.12)	.254
≥100 000	0.90 (.26–3.18)	.873	1.21 (.25–5.99)	.813
CD4 cell count, cells/mm^3[c]				
0–200 (reference)	1.00		1.00	
200–499	1.07 (.95–1.20)	.256	0.94 (.79–1.11)	.472
≥500	1.21 (1.07–1.36)	.003	0.99 (.83–1.19)	.927
NRTIs, yes vs no	0.67 (.55–.81)	.000	0.78 (.58–1.04)	.094
NNRTIs, yes vs no	0.73 (.68–.79)	.000	0.98 (.87–1.11)	.774
FIs, yes vs no	1.08 (.70–1.67)	.735	0.74 (.41–1.35)	.324
EIs, yes vs no	1.69 (1.08–2.64)	.021	0.59 (.31–1.12)	.107
INSTIs, yes vs no	1.80 (1.58–2.05)	.000	1.49 (1.22–1.83)	.000
PIs, yes vs no	1.69 (1.56–1.83)	.000	1.82 (1.61–2.05)	.000

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EIs, entry inhibitors (maraviroc); FIs, fusion inhibitors (enfuvirtide); HIV, human immunodeficiency virus; INSTIs, HIV integrase strand transfer inhibitors (raltegravir); NNRTIs, nonnucleoside reverse-transcriptase inhibitors (efavirenz, etravirine, delavirdine, nevirapine, rilpivirine); NRTIs, nucleoside reverse-transcriptase inhibitors (abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, zidovudine); OR, odds ratio; PIs, protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir); TDF, tenofovir disoproxil fumarate.

[a] The multivariate model included variables measured at baseline: eGFR, sex, race, sexual orientation, monthly income, type of employment, smoking and injection drug users as well as time-varying variables: TDF exposure, age, alcohol consumption, diabetes, hypertension, viral load, CD4 cell count, and use of NRTIs, NNRTIs, FIs, EIs, INSTIs, or PIs. A total of 1043 patients were included in analysis because they had ≥1 eGFR measurement. Outcome was defined as eGFR <90 mL/min/1.73 m^2.

[b] Categorization based on clinical significance.

[c] Categorization based on World Health Organization guidelines.

years (the mean loss attributable to TDF was lower after 3 years than after 1 or 2 years).

This analysis calculated the mean loss for the entire cohort; one might wonder about the possible individual variability, that is, whether the effect might be large in a small group. However, the standard deviation, median, and IQR for the exposed and unexposed groups were comparable. For example, after ≥6 years of TDF, a mean loss of −10.46/min/

Table 4. Loss in Estimated Glomerular Filtration Rate: Crude Mean and Univariate and Multivariate Linear Regression Analysis, by Tenofovir Disoproxil Fumarate Exposure

	Exposed		Unexposed		Univariate Linear Regression Analysis		Multivariate Linear Regression Analysis[a]	
Cumulative Exposure	No.	Mean Loss in eGFR[b] (95% CI)	No.	Mean Loss in eGFR (95% CI)	Loss in eGFR[b] Attributable to TDF (95% CI)	*P*	Adjusted Loss in eGFR[b] Attributable to TDF (95% CI)	*P*
After 1 y	483	−3.31 (−5.02 to −1.60)	389	−0.25 (−2.02 to 1.51)	−3.08 (−5.55 to −.60)	.015	−3.05 (−5.55 to −.54)	.017
After 2 y	358	−5.79 (−7.00 to −4.58)	344	−1.66 (−3.22 to −.10)	−4.16 (−6.12 to −2.20)	.000	−4.05 (−6.03 to −2.08)	.000
After 3 y	241	−6.44 (−8.00 to −4.88)	283	−3.76 (−5.13 to −2.38)	−2.75 (−4.75 to −0.61)	.009	−2.42 (−4.57 to −.28)	.023
After 4 y	149	−8.27 (−10.62 to −5.92)	224	−5.14 (−7.80 to −2.48)	−3.15 (−6.92 to 0.61)	.101	−3.09 (−6.98 to .80)	.119
After 5 y	78	−8.61 (−11.69 to −5.53)	168	−7.73 (−9.51 to −5.95)	−0.88 (−4.21 to 2.45)	.602	−0.12 (−3.59 to 3.35)	.946
After ≥6 y	32	−10.46 (−15.43 to −5.49)	143	−9.42 (−11.45 to −7.39)	−1.05 (−5.90 to 3.80)	.671	0.32 (−4.55 to 5.19)	.898

Patients with estimated glomerular filtration (eGFR) rates <90 mL/min/1.73 m^2 at baseline were not excluded; 872 patients were included in this analysis because they had adequate measurement of eGFR at beginning of exposure (to tenofovir disoproxil fumarate or other antiretroviral) and were exposed for ≥1 year.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); TDF, tenofovir disoproxil fumarate.

[a] Empirical control of confounders was done using the ±5% change in estimates method (if the inclusion of the covariable in the model changed the estimate by 5%, the variable was kept in the multivariate model), considering variables measured at the beginning of exposure to TDF or other antiretrovirals (eGFR, alcohol consumption), variables measured at baseline (age, sex, race, sexual orientation, monthly income, type of employment, smoking), and variable measured during follow-up (period prevalence; injection drug use, diabetes, hypertension, and use of nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors [NNRTIs], fusion inhibitors, entry inhibitors, human immunodeficiency virus integrase strand transfer inhibitors, or protease inhibitors [PIs]). Variables (confounders) included in the model were eGFR at baseline and use of NNRTIs or PIs.

[b] Loss in eGFR directly attributable to TDF exposure.

1.73 m^2 was observed in exposed patients (SD, 14.00, median, −8.76; IQR, −18.51 to −3.31), whereas in patients exposed to other ARVs it was −9.42 mL/min/1.73 m^2 (SD, 12.50; median, −8.56; IQR, −17.62 to −1.20).

As in other studies, we found an increased risk of renal dysfunction in older patients, those with a lower eGFR at baseline, and those exposed to PIs, as well as a reduced risk with NRTI use [3, 5, 7, 10, 6]. Surprisingly, however, in the GEE models, we found a negative association with black race and smoking as well as a positive association with INSTI use, contrary to what is reported in the literature [19–23]. One possible reason for the negative association with black race is the adjustment for race in the formulas used to estimate the glomerular function rate, such as CKD-EPI or MDRD. Black patients are scored higher than those of other races to compensate for their lower glomerular function rate. It is therefore to be expected that regression models using eGFR as the dependant variable will find a negative association with black race. The same results were observed recently in the large D:A:D cohort study [12].

Our study has strengths and limitations. One of the strengths is the long follow-up period. The sample was also of considerable size. Furthermore, ours is a real-life cohort including older patients, making the results more generalizable to a clinic-based cohort of HIV-positive patients, although there was a low number of black and female patients. The cohort was essentially composed of white homosexual men and included a large proportion of IDUs. Among the limitations are also the observational design (nonrandomized) and the potential for the presence of confounding by indication. However, we made a very conservative adjustment for potential confounding in every multivariate model. Although it would have been interesting to include hepatitis C status (variable not collected), most of its potential confounding effect might be controlled with the inclusion of injection drug use in the models. We also controlled for monthly income and type of employment, which are known to reflect global health and lifestyle. Also, it would have been interesting to analyze the association between TDF and renal function in our cohort using an eGFR <60 mL/min/1.73 m^2. However, few patients in our clinic-based cohort had this outcome, because eGFR seldom goes below 60 mL/min/1.73 m^2 without changes in ART. Because we used a cut point at 90 mL/min/1.73 m^2, our study demonstrated a loss of kidney function and not chronic kidney disease as formally defined by the National Kidney Foundation [18]. Moreover, it would have been interesting to have results on urinalysis or proteinuria, but these data were not available. In addition, although the sample was large, we did not have the power to look at the impact of every ARV taken individually.

Another limitation was the lack of power to evaluate the loss in eGFR attributable to TDF after >4 years of exposure. Although the loss in eGFR attributable to TDF seems to occur during the first year and then stay relatively stable after that, it is not possible to draw definite conclusion about the magnitude of the effect after 4 years of exposure. This needs to be

elucidated. Furthermore, it is possible that we underestimated the loss in eGFR attributable to TDF, because patients in the TDF-exposed group may have been more likely to experience significant changes in eGFR and to switch to alternative ARTs, leaving patients with more stable eGFRs in the analysis. Finally, a large number of patients were excluded from the analysis because they had not visited the clinic within the last 2 years. However, they were very similar at baseline to the active patients in term of age and sex (data not shown). CD4 cell counts (cells/mm^3) were also similar (471 [IQR, 310–680] for excluded patients vs 480 [260–900] for included patients). The median viral loads at baseline differed slightly, at 2506 HIV RNA copies/mL (49–27 851) for excluded patients and 1550 HIV RNA copies/mL (49–42 285) for active patients. It is possible that excluded patients were less "healthy," which may have affected the results of the study.

There has been debate about the association between TDF exposure and renal dysfunction and about the clinical impact of the loss in eGFR due to TDF exposure. Our study shows that the association was not of a high magnitude and that the quantified loss in eGFR attributable to TDF is relatively modest after many years of exposure. Importantly, the loss attributable to TDF seems to occur during the first year of exposure and stabilizes after that. Although the loss is maintained, it does not seem to further deteriorate with additional years of exposure. The clinical impact of this association need to be analyzed, taking into account the efficacy of TDF, but it is highly plausible that TDF exposure, although associated with reduced kidney function, has no severe adverse effects over the long term for most HIV-positive patients.

Notes

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