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Short Communication

High rate of reversibility of renal damage in a cohort of HIV-infected patients receiving tenofovir-containing antiretroviral therapy

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ABSTRACT

We assessed the progress of renal damage after discontinuation of tenofovir (TDF) in patients who started therapy with normal renal parameters. Normal local reference values were as follows: estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation (MDRD), ⩾60 mL/min/1.73 m^2; creatinine, ⩽1.20 mg/dL; serum phosphate: ⩾2.69 mg/dL; proteinuria: <30 mg/dL, and glycosuria: <20 mg/dL in nondiabetic patients. A logistic regression analysis was used to evaluate factors related to normalization of renal function.

We included 183 patients; 85% were male, and median (IQR) age was 44 (40–50) years. Time on TDF was 39 (22–63) months. After 22 (13–49.5) months from TDF discontinuation, renal parameters returned to normal values in 59% of patients, improved (without reaching normal values) in 9.8%, and did not improve in 31%. Median time until normalization was 4 (2–15.75) months, and time to maximum improvement in patients whose values did not return to normal was 14 (8.75–27.75) months. Follow-up was <12 months in 30% of the patients who did not improve. The only factors significantly associated with normalization of renal parameters were nadir CD4 T-cell count ($p = 0.034$; OR = 1.002, per 1 cell of increase) and CD4 T-cell count at the end of therapy with TDF ($p = 0.030$; OR = 1.033, per 1 cell of increase). Reversibility of renal damage was prompt and complete in 59% of patients receiving TDF-containing regimens and was associated with a higher nadir and current CD4+ T-cell count, suggesting a role of preserved cellular immunity in renal recovery in this population.

The nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF) has potent activity against the human immunodeficiency virus type 1 (HIV-1) and low toxicity. However, some patients develop nephrotoxicity, which can lead to discontinuation in 1–2% (Campbell et al., 2009; Cihlar and Ray, 2010; Choi et al., 2009; Davidson et al., 2010; Gupta et al., 2005; Hawkins, 2010; O'Donnell et al., 2011). TDF is excreted by the kidneys via a combination of glomerular filtration and active tubular secretion. Intracellular accumulation of TDF is responsible for damage to tubular cells (Cihlar and Ray, 2010; Wyatt et al., 2007). Consequently, nephrotoxicity is usually presented as tubular dysfunction, which can, in turn, lead to Fanconi syndrome (Choi et al., 2009; Mocroft et al., 2007).

Although the prevalence and type of TDF-induced renal impairment are clearly defined, (Gallant et al., 2004; Izzedine et al., 2005) findings on renal function once TDF is discontinued are both scarce and controversial. (Kapitsinou and Ansari, 2008; Wever et al., 2010; Wood et al., 2009) Some studies report reversibility of TDF-associated renal damage after interruption of the drug, (Izzedine et al., 2004; Kapitsinou and Ansari, 2008; Verhelst et al., 2002) whereas others conclude that impairment could be irreversible (Scherzer et al., 2012). The prevalence of permanent TDF-induced renal impairment and the predisposing factors for complete recovery should be well established, since this alteration is associated with increased morbidity and mortality (Drey et al., 2003; Muntner et al., 2002).

We performed a retrospective observational study of all patients attending our HIV Unit who discontinued TDF-containing regimens with renal impairment to assess the outcome of renal injury and to identify factors related to complete renal recovery after discontinuation. Patients receiving a TDF-containing regimen for at least three months and starting TDF with normal renal parameters but who developed renal impairment and discontinued TDF were included in the study. Patients with no available data on renal outcome after interruption of TDF were excluded.

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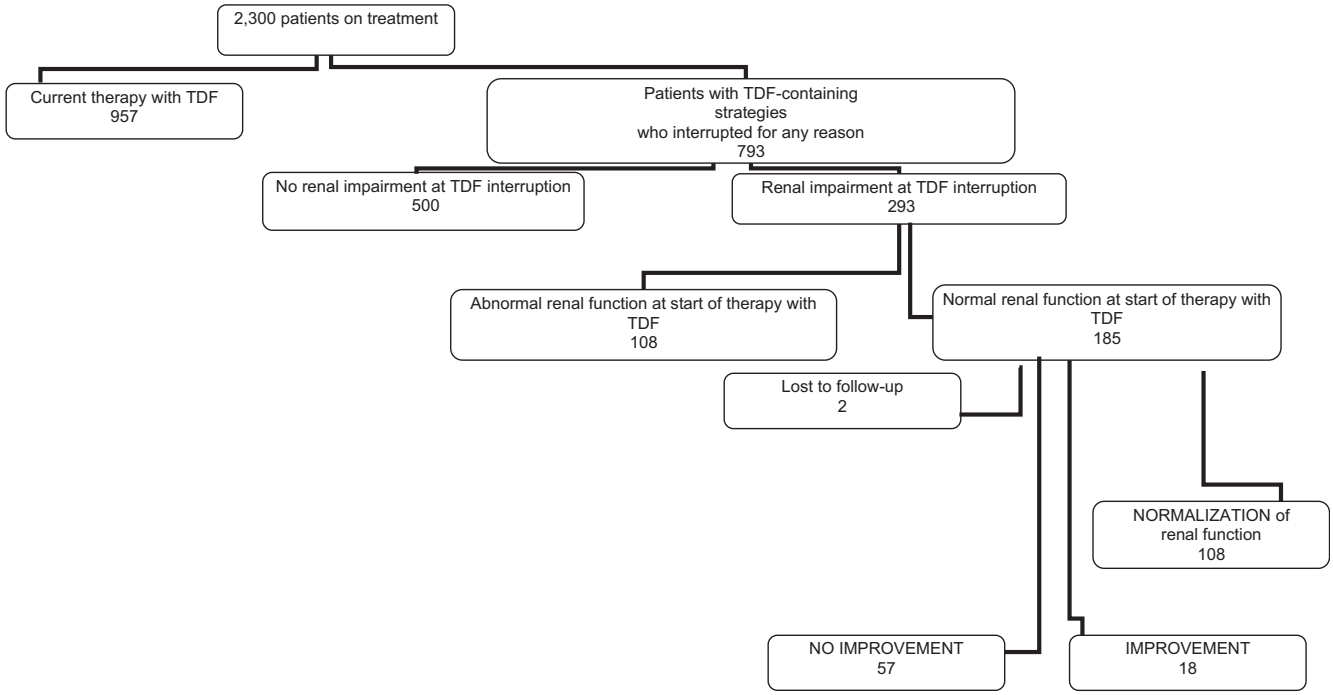

Fig. 1. Flow chart. Patient selection process.

Table 1
Baseline characteristics of the patients.

	N = 183
Gender (male), *n* (%)	157 (85%)
Caucasian, *n* (%)	178 (96%)
Hepatitis B or C coinfection	71 (38.8%)
Age, years	44 (40;50)
Time since HIV diagnosis, years	13.3 (8.8;17.2)
CD4+ T-cell count at initiation of TDF, cells/μL	294 (118.5;488)
CD4+ T-cell count at discontinuation of TDF, cells/μL	456 (306.5;638)
Nadir CD4+ T-cell count, cells/μL	177 (76.5;279)
Time on antiretroviral treatment, months	141 (92;171.5)
Time on protease inhibitors, months	75.5 (38;122)
Time on TDF, months	39 (22;63)
Hepatitis B/C coinfection	71 (38.8%)
Change of treatment when TDF is discontinued	
Only stop TDF, *n* (%)	92 (50%)
Switch to ABC, *n* (%)	52 (28%)
Discontinuation of the PI when TDF is discontinued, *n* (%)	13 (7%)
Change of TDF to another NRTI, *n* (%)	26 (14%)
Arterial hypertension (*n* = 131[a])	27 (20.6%)
Diabetes (*n* = 131[a])	12 (9%)

IQR, interquartile range; PI, protease inhibitors; TDF, tenofovir; ABC, abacavir; *n*, number of patients; NRTI, nucleotide reverse transcriptase inhibitor.
Data are expressed as the median (IQR) unless otherwise indicated.
[a] Patients with this data available.

Serum creatinine and phosphate, glycosuria and proteinuria (urine dipstick), and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation (MDRD) were recorded at initiation of TDF treatment, during treatment and after discontinuation of TDF (until the most recently available data). Demographic, clinical, and HIV-related data were also collected from the patient's clinical notes.

According to the local reference values, renal impairment was defined as the presence of at least one of the following conditions in two consecutive determinations: abnormal creatinine values (>1.20 mg/dL), abnormal serum phosphate values (<2.69 mg/dL), eGFR <60 mL/min/1.73 m^2, proteinuria ($\geqslant$30 mg/dL), or glycosuria ($\geqslant$20 mg/dL, in nondiabetic patients). eGFR were considered normal when >60 mL/min/1.73 m^2; in such cases, no numerical values were provided due to the inaccuracy of this formula when eGFR is >60 mL/min/1.73 m^2 in populations without chronic kidney disease (Poggio et al., 2005; Rule et al., 2004; Stevens et al., 2006), MDRD was considered abnormal if <60 mL/min/1.73 m^2, in this case, numerical value were provided.

Renal outcome after discontinuation of TDF was classified as normalization, improvement, or irreversible damage. The return to the baseline normal values in all renal parameters and its persistence until the last observation was considered normalization. Patients who return to the baseline normal values in all renal parameters and persistence on normal values until the last observation was considered were considered *Normalization*. When renal parameters improved but without achieving normal values, it was considered *Improvement*. Then, *Improvement* was defined as follows: increase in GFR until 60 mL/min/1.73 m^2 (but not >60 mL/min/1.73 m^2, in this case it would be considered *Normalization*); decrease in creatinine value to 1.20 mg/dL, but not <1.20 mg/dL; increase in serum phosphate levels to 2.69 mg/dL (but not >2.69 mg/dL); decrease in proteinuria: to 30 mg/dL but not <30 mg/dL, and decrease in glycosuria to 20 mg/dL but not <20 mg/dL. Finally, renal damage was considered irreversible when the patient did not present any improvement in any of the altered parameters observed at discontinuation of TDF. Time to normalization was considered the first time at which patients returned to normal range values for all renal parameters after interruption of TDF and their persistence over time. Time to improvement was considered the first time at which patients achieved consistently better values in any renal parameter.

The mean, standard deviation (SD), median (IQR), and frequency (%) were used to describe patient characteristics. A descriptive data analysis was performed to identify time to normalization or time to maximum improvement. A logistic regression model (Cox regression model) was constructed to determine which factors were associated with normalization. This analysis included the following variables: time since diagnosis of HIV, CD4 T-cell count at the beginning and end of the TDF-containing regimen, nadir CD4 T-cell count, months on antiretroviral treatment, months on

Table 2
Outcome of renal parameters.

	Discontinuation of TDF	End of follow-up
Creatinine, median (IQR), mg/dL	*n* = 183 1.27 (1.22;1.38)	*n* = 183 0.97 (0.84;1.10)
Abnormal creatinine values, *n* (%)	152 (87.4%)	26 (14%)
Abnormal MDRD, median, (IQR)	*n* = 159 53 (42;56.25)	*n* = 183 NA
Abnormal MDRD, *n* (%)	33 (20.75%)	12 (7.5%)
Serum phosphate levels, mg/dL, median (IQR)	*n* = 118 3.09 (2.85;3.50)	*n* = 118 3.13 (2.66;3.6)
Abnormal phosphate levels, *n* (%)	23 (19.5%)	30 (25.4%)
Proteinuria, *n* (%)	*n* = 32 10 (32.2%)	*n* = 86 21 (24.4%)
Degrees of proteinuria in patients with abnormal values		
⩾30 < 100 mg/dL	7 patients	8 patients
⩾100 < 500 mg/dL	1 patient	7 patients
⩾500 mg/dL	2 patients	6 patients
Glycosuria, *n* (%)	2 (6.25%)	0
Degrees of glycosuria in patients with abnormal values		
⩾50 < 150 mg/dL	1 patient	
⩾150 < 500 mg/dL	1 patient	

TDF, tenofovir; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease equation; *n*, number of patients; NA, not applicable (all patients with normal values).

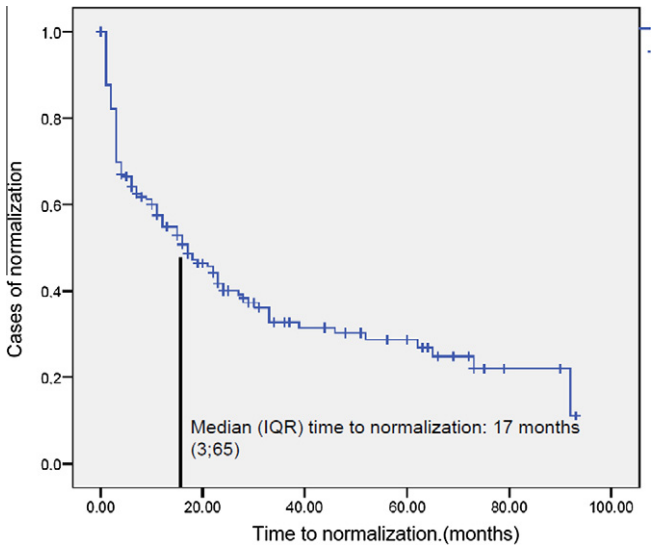

Fig. 2. Kaplan–Meier plot of the evolution to normalization of the total patient population.

protease inhibitors, and months on TDF. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). A *p* value less than 0.05 was considered statistically significant.

Our HIV Unit attends 2,300 patients receiving antiretroviral therapy, of whom 793 had previously received a TDF-containing regimen and subsequently interrupted the drug (any reason). Of this group, 293 fulfilled the criteria for renal impairment while taking TDF (37%), but only 185 out of 293 had started TDF with a normal renal function (23%). Two patients from this group were lost to follow-up, and no data were available after discontinuation of TDF. The final study sample comprised 183 patients (Fig. 1).

Patient characteristics are summarized in Table 1. Median time on TDF-containing regimens was 39 months (22–63), and 133 patients (72.6%) included protease inhibitors (PIs) in their TDF-containing strategies. Comorbid conditions were available from the clinical notes for a total of 131 patients (71.6%).

After a median of 22.5 (13–49.5) months of follow-up after discontinuation, 108 patients out of 183 (59%) presented normal values in all the renal parameters evaluated. Improvement without achieving normal values was observed in 18 patients (9.8%). Finally, 57 patients (31%) had no improvement in any parameter. With respect to the proportion of change from baseline values, the median (IQR) change in creatinine at the end of follow-up with respect to baseline was −0.294 (−0.407 to −0.170) mg/dL. The normal reference range was reached by 158 patients (86%); 16 patients did not have improved creatinine values at the end of follow-up (8.7%). The median (IQR) change in phosphate levels was 0.526 (0.031–0.774) mg/dL. This parameter returned to normal values in 4 patients (17%), improved in 15 (65%), and worsened in 4 patients (17%) at the end of follow-up. Values returned to normal in 50% of patients with proteinuria and improved in 30%. The outcome of renal parameters is summarized in Table 2.

In the overall sample, Kaplan–Meier analysis estimated that median time to normalization was 17 (IQR 3–65) months (Fig. 2). With respect to the group whose values returned to normal, time to normalization was 4 (2–15.75) months, and median time of maximum improvement in patients whose values improved but did not return to normal was 14 (8.75–27.75) months. With regard to the 57 patients whose abnormal renal parameters did not improve, 17 (30%) had less than 12 months of follow-up. Of these, 9 (16%) had a maximum of 6 months of follow-up.

The variables associated with complete recovery after discontinuation of TDF were nadir CD4 T-cell count ($p = 0.034$; OR = 1.002) and CD4 T-cell count at the end of therapy with TDF ($p = 0.030$; OR = 1.033). Associations with other demographic, clinical, and AIDS-related conditions did not achieve statistical significance (Table 3).

Rates of reversibility after discontinuation in our cohort (normal or improved renal values in 69% of our patients; no improvement in 31%) are similar to those of the largest published study evaluating renal function after discontinuation of TDF (Wever et al., 2010) but lower than those of other studies (Izzedine et al., 2004; Kapitsinou and Ansari, 2008; Verhelst et al., 2002; Zimmermann et al., 2006). Differences between our and other data could be related to the different durations of exposure to the drug. TDF-related nephropathy is mediated by intracellular accumulation in the proximal renal tubules that leads to mitochondrial injury and mtDNA depletion (Kohler et al., 2009). Consequently, more time on TDF-containing regimens, as in our cohort, may lead

Table 3
Logistic regression analysis. Variables associated with complete recovery.

HIV or clinical condition	*p* value	Odds ratio (95% CI)
AIDS condition (present)	0.127	0.550 (0.255; 1.186)
Gender (male)	0.843	0.920 (0.404; 2.095)
Age (year)	0.076	0.970 (0.938;1.003)
Hepatitis B/C coinfection	0.754	0.890 (0.429;1.846)
Years with HIV infection	0.115	0.952 (0.913;1.010)
CD4 T-cell count at the beginning of TDF use	0.085	1.026 (0.996;1.056)
CD4 T-cell count at discontinuation of TDF (per 1 unit of increase)	**0.030**	**1.033 (1.003;1.063)**
Nadir CD4 T-cell count (per 1 unit of increase)	**0.034**	**1.002 (1.000;1.005)**
Time on antiretroviral therapy (months)	0.097	0.996 (0.991;1.001)
Time on PIs (months)	0.293	0.997 (0.991;1.003)
Time on TDF (months)	0.237	0.993 (0.982;1.004)

Statistically significant *p* values are shown in bold. The OR for the covariates is given per 1 unit; in the case of CD4 T-cell counts, the OR for the covariate is expressed per 1 unit (1 cell/μL) of increase. PIs, protease inhibitors; TDF, tenofovir.

to greater drug-related toxicity and irreversible mitochondrial damage. Moreover, genetic variants in *ABCC10*, a TDF transporter, are more frequently involved in TDF-related nephrotoxicity (Pushpakom et al., 2012; Rodriguez-Novoa et al., 2009). In addition, the concomitant use of protease inhibitors and TDF leads to more severe renal damage resulting from increased intracellular accumulation of TDF, and most of our patients were on PI-containing regimens. Finally, the higher median age of our patients (56 versus 44 years in others) (Wever et al., 2010) could also explain our different results; older age is associated with a decrease in GFR (Wetzels et al., 2007) and with a negative impact on recovery from mitochondrial damage.

Patients in whom all parameters returned to normal values had a very quick complete renal recovery (4 months), but the time to improvement was much longer after discontinuation of TDF in the remaining patients. Nevertheless, 30% of our patients who did not reach normal renal parameters had a short follow-up (less than 12 months); consequently, our analysis probably underestimates the proportion of patients whose renal parameters returned to normal or improved.

High nadir CD4 T-cell counts and current CD4 T-cell counts were the only factors significantly associated with complete renal recovery, confirming previous observations (Gallant et al., 2005). Low nadir CD4 T-cell count is associated with higher rates of complications in HIV-infected patients, including neurocognitive impairment (Munoz-Moreno et al., 2008) low bone mineral density (Bonjoch et al., 2010b) and cardiovascular events (Ho et al., 2010). A worse prognosis in patients with low nadir CD4 T-cell counts could be a consequence of greater difficulty in achieving a suitable CD4 T-cell recovery (Negredo et al., 2010). Additionally, subjects with low CD4 T-cell counts usually present elevated immune activation (Massanella et al., 2010), even in patients with prolonged viral suppression (Kamat et al., 2012). High levels of chronic immune activation and systemic inflammation are related to more overall toxicity and, specifically, could favour the TDF-related toxicity (Brown et al., 2011). Our results for renal parameters are consistent with these data; patients with lower nadir and current CD4 T-cell counts showed a low rate of recovery from renal injury, probably because levels of immune activation and inflammation were higher in this population than in patients with a better immune status, promoting more toxicity.

The retrospective design of the study meant that data on comorbidities or other conditions with renal impact were available from most but no all participants. This limitation may lead to an overestimation of the role of TDF in renal impairment. Patients with abnormal renal function at initiation of TDF were excluded from our analysis to facilitate detection of any potential association between renal damage and TDF. However, the presence of concomitant conditions with a negative impact on renal function could also play an important role and prevent or slow renal recovery after discontinuation of TDF. A second limitation of the present study may be the incomplete analysis of tubular dysfunction (which did not include fractional excretion of phosphate and partially included serum phosphate levels, glycosuria, and proteinuria) in some patients, mainly during the earlier part of the study (before initiation of TDF), when a detailed renal workup was not generally available. Insufficient data in this regard could mask the real extent of renal abnormalities at baseline. In addition, the MDRD equation shows inaccuracy in some populations if values are >60 mL/min/1.73 m^2 (Stevens et al., 2006) and, as a consequence, the lack of precision may not allow to clearly determine the evolution of GFR. In addition, other measurements that showed a strong correlation in these cases (values >60 mL/min/1.73 m^2), or that showed a high correlation with isotopic GFR in the HIV-infected population, such as cystatin C (Bonjoch et al., 2010a), were not available in our study.

In conclusion, we provide useful clinical data on the outcome of renal damage in a large group of patients who presented renal abnormalities under TDF-containing regimens and discontinued the drug. Renal recovery was usually rapid and complete, although it took longer and was only partial in some patients. Nadir and current CD4 T-cell count during therapy with TDF play a crucial role in renal recovery. Since data on the reversibility of TDF-induced renal impairment are scarce, long-term prospective studies are necessary to corroborate our findings on reversibility and on predisposing factors for irreversibility of renal impairment, as well as to identify those patients in whom TDF does not cause permanent renal damage.

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