Renal Impairment in Patients Receiving a Tenofovir-cART Regimen: Impact of Tenofovir Trough Concentration

Isabelle Poizot-Martin, MD, Caroline Solas, PhD,† Julie Allemand, MD,* Véronique Obry-Roguet,* Vincent Pradel, MD,‡ Sylvie Bregigeon, MD,* Olivia Faucher, MD,* and Bruno Lacarelle, PharmD, PhD†*

Objective: Tenofovir disoproxil fumarate (TDF) is known to induce renal dysfunction in HIV-infected patients. The aim of this retrospective study was to evaluate the correlation between TDF trough concentration (Ctrough-TDF) and glomerular filtration rate (GFR) in a cohort of patients on antiretroviral therapy.

Methods: A total of 163 patients with at least one determination of Ctrough-TDF between 17–24 hours were retrospectively selected from a computerized database and distributed into 3 groups defined by TDF concentrations <40 (11.7%), between 40 and 90 (36.8%), and >90 (high-level group, 51.5%) ng/mL. GFR was measured by Cockcroft–Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration formulae at the times of TDF initiation and Ctrough-TDF determination and after 12 months.

Results: At the time of Ctrough-TDF measurement, median duration of TDF-based therapy was 21.1 months. GFR was significantly decreased in high-level group (−8.5 mL/min; $P < 0.001$) whatever the method used. GFR decline was significantly associated with an older age. Gender-stratified analysis showed that the early impact of Ctrough-TDF >90 ng/mL was significant in women only. After 12 months, the decrease in GFR in patients with high Ctrough-TDF was observed in both men and women (−8.27; $P = 0.003$).

Conclusions: The high prevalence of elevated Ctrough-TDF and its correlation with an increased risk of renal impairment support the usefulness of therapeutic drug monitoring for TDF, particularly in women and older patients.

Received for publication March 22, 2012; accepted November 6, 2012.

From the *Aix-Marseille University, APHM Sainte-Marguerite, Service d'Immuno-Hématologie Clinique, INSERM U912 (SESSTIM), Marseille, France; †Aix-Marseille University, APHM La Timone, Laboratoire de Pharmacocinétique et de Toxicologie, CRO2-INSERM, UMR911, Marseille, France; and ‡Département de Biostatistique et Informatique Médicale, Centre Hospitalo-Universitaire Sainte Marguerite, Marseille, France.

Data partly presented at the XVIII Conference on Retrovirus and Opportunistic Infections, March 2, 2011, Boston, MA.

The authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Isabelle Poizot-Martin, MD, Service d'Immuno-Hématologie Clinique, Centre d'Informations et de Soins de l'Immunodéficience Humaine et des Hépatites Virales (CISIH), Hôpital Sainte-Marguerite, 270, Boulevard Sainte-Marguerite, 13009 Marseille, France (e-mail: isabelle.poizot@mail.ap-hm.fr).

Key Words: tenofovir, HIV, antiretroviral therapy, renal toxicity, glomerular function

(*J Acquir Immune Defic Syndr* 2013;62:375–380)

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse-transcriptase inhibitor (NRTI) approved for the treatment of HIV infection. TDF-based regimens are widely used and represent recommended antiretroviral options for a large number of patients worldwide.[1,2]

TDF undergoes renal clearance by a combination of glomerular filtration and active tubular secretion.[3] A decline of renal function and a proximal tubular dysfunction, including the development of a Fanconi syndrome, have been reported in patients initiating therapy with a TDF-based regimen, which are expected to develop over time.[4–8] While the exact mechanism of this toxicity remains unclear, a subcellular decrease in mitochondrial DNA abundance has been recently described in mice as being involved in TDF-induced renal tubular toxicity.[9] Several associated risk factors have been proposed, which include genetic predisposition (ABCC2 gene)[10] and the combination with some ritonavir-boosted protease inhibitor (PI/r), expected to increase TDF plasma concentration and the risk of TDF-induced renal toxicity.[4,11,12] Recently, Rodríguez-Nóvoa et al[13] showed a dose-dependent effect of TDF plasma concentrations on kidney tubular dysfunction, which suggested that therapeutic drug monitoring of TDF might be useful to prevent renal toxicity and optimize TDF tolerance. On the other hand, several studies reported a greater effect of TDF on the decline in renal function.[7,14]

The objective of this study was to explore the correlation between TDF plasma trough concentration (Ctrough-TDF) and glomerular function in a population of patients on a combination of antiretroviral therapy (cART) containing TDF and to isolate independent variables predicting TDF-induced renal dysfunction.

METHODS

This study was performed in an outdoor HIV clinical unit, where approximately 1000 patients [40% hepatitis C virus (HCV) coinfected] are followed. Data of HIV-infected patients receiving a TDF-containing cART regimen between December 2006 and January 2010 were retrospectively collected from the Nadis electronic medical record database.[15]

Patients with ≥1 available measurement of Ctrough-TDF performed at steady state and at least 17 hours after drug intake were included in the analysis. When several measurements were available, the highest value was retained for the analysis. In France, because of possible TDF-induced renal impairment, TDF monitoring is usually done on the occasion of renal function assessment (performed every month during the first year after TDF introduction). Information about the time of last drug intake was reported at the time of sample collection. Patients taking drugs expected to induce nephrotoxicity (eg, amphotericin B and nonsteroidal anti-inflammatory drugs) were excluded.

Main Outcome Measures

Ctrough-TDF was quantified by a validated high-performance liquid chromatography method (limit of quantification: 40 ng/mL, according to the ongoing Food and Drug Administration guidelines for bioanalytical method validation) with an expected interval ranging between 40 and 90 ng/mL according to the lower and upper limits mentioned in the summary of TDF characteristics.[16]

The main parameter monitored to assess renal function was glomerular function rate (GFR) assessed by creatinine clearance calculated with the Cockroft and Gault (CG)[17] formula, and also by using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[18] Renal impairment was defined as GFR <60 mL/min. Renal filtration rate was assessed at the time of TDF initiation (BL-GFR), at the time of Ctrough-TDF determination (T1-GFR), and for patients still on the same cART, 12 months later (T2-GFR).

Patients were distributed into 3 subgroups according to Ctrough-TDF. Low-level (LL), normal-level (NL), and high-level (HL) groups were defined by Ctrough-TDF <40, between 40 and 90, and >90 ng/mL, respectively.

Other variables included in the analysis were age, gender, weight, body mass index, corporal surface, comorbidities (hypertension, diabetes, and hepatitis C), Centers for Disease Control and Prevention stage, time of exposure to TDF, association of a PI/r or atazanavir (boosted or not boosted by ritonavir), plasma HIV viral load, CD4 counts, and phosphoremia measured in the fasting state (normal values = 0.78–1.53 mmol/L). All those variables were collected at the time of Ctrough-TDF determination.

Statistical Analysis

Median values and interquartile ranges (IQRs) (first and third quartiles) were calculated for the description of quantitative variables. The χ^2 test (or Fisher exact test, when χ^2 test was not applicable) was used to compare proportions. The Kruskal–Wallis and Mann–Whitney nonparametric tests were used for group comparison of quantitative variables. A multivariate analysis to identify the variables associated with GFR changes was performed by using a linear regression model, adjusting to baseline GFR values, and testing for interactions. All significance levels were set at 0.05. Statistical analyses were performed using SPSS software, version 15 (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

In this retrospective study, 168 patients receiving a TDF-based regimen were identified. Five patients were excluded because of chronic renal failure or concomitant administration of other nephrotoxic drugs. The remaining 163 patients were included in the analysis. Several plasma TDF measurements, performed in 51 patients, showed that Ctrough-TDF was relatively stable over the follow-up period, indicating a low intraindividual variability. Moreover, although only one value was retained, Ctrough-TDF was always >90 ng/mL in patients from the HL group. At the time of Ctrough-TDF determination, the median time since HIV diagnosis was around 17 years (IQR: 11.3–21.1), and 13% of the patients had progressed to AIDS. The median duration of ART was 8.7 years (IQR: 4.3–11.9), and the median period of TDF-based therapy was 21.1 months (IQR: 0.3–89.8). One-quarter of the population was coinfected with HCV, whereas diabetes and hypertension were reported in approximately 14% of the patients. The median value of CD4 counts was 382 cells/mm^3 (IQR: 236–586) and 68% of the patients had an undetectable plasma viral load (<40 copies/mL). The cART regimens included non-NRTI (NNRTI) in 15% of the patients; PI/r in 64%, which consisted of atazanavir/r (45%), darunavir/r (13%), fosamprenavir/r (10%), lopinavir/r (8%), or saquinavir/r (2%); nonboosted atazanavir in 8%, whereas 13% of the patients were treated with other TDF containing-regimens.

Distribution of Ctrough–Tenofovir Disoproxil Fumarate

Median Ctrough-TDF in the whole population was 92 ng/mL (IQR: 61–135) and was not influenced by gender [men, n = 99, 100 ng/mL (IQR: 72–135); women, n = 45, 106 ng/mL (IQR: 74–164); P = 0.465]. Median Ctrough-TDF was higher in patients treated with PI/r but the difference did not reach statistical significance [NNRTI-combined regimen: 85 ng/mL (IQR: 73–126); PI/r-combined regimen: 103 ng/mL (IQR: 73–149); P = 0.461]. The proportions of patients in LL, NL and HL groups were 11.7% (n = 19), 36.8% (n = 60), and 51.5% (n = 84), respectively. Median Ctrough-TDF in NL and HL groups were 70 ng/mL (IQR: 55–78) and 130 ng/mL (IQR: 106–178), respectively. Ctrough-TDF values in LL group were <40 ng/mL, which is the limit of both the expected interval and quantification. As shown in Table 1, the 3 groups were comparable with respect to gender ratio, age, body mass index, and corporal surface. Regarding common renal impairment risk factors, the prevalence of diabetes, hypertension, or HCV coinfection was not statistically different between groups. There was no association between Ctrough-TDF and the time exposure to TDF. Although the proportion of TDF-NRTI + NNRTI regimens varied among groups, the proportions of patients receiving a PI/r based regimen were similar in the 3 groups (between 63% and 74%). Centers for Disease Control and Prevention stages were significantly different but had no correlation with the Ctrough-TDF. Median viral load and CD4 cell count and the nadir of CD4 cell count were comparable in the 3 groups.

TABLE 1. Distribution of Common Renal Impairment Risk Factors According to Ctrough-TDF at the Time of TDF Concentration Determination (T1)

Median (IQR) or Percentage (When Indicated)	LL Group (n = 19)	NL Group (n = 60)	HL Group (n = 84)
Age, yrs	48 (43–51)	46 (41–51)	47 (42–52)
Females, %	21.1	30.0	32.1
BMI, kg/m^2	21.3 (17.8–23.0)	22.4 (19.8–25.6)	21.0 (19.6–23.3)
Corporal surface, m^2	1.76 (1.62–1.87)	1.78(1.65–1.94)	1.74 (1.59–1.85)
ART-regimen, %*			
TDF + NRTI + IP	73.7	56.7	63.1
TDF + NRTI + NNRTI	0	25.0	13.1
TDF exposure, mo	26.1 (3.3–42.3)	19.2 (6.0–50.4)	18.1 (2.6–46.2)
Hypertension, %	15.8	13.3	14.5
Diabetes, %	10.5	13.3	16.7
PCR HCV+, %	36.8	27.1	22.6
CDC stage, %†			
A	21.1	33.3	28.6
B	36.8	56.7	32.1
C	42.1	10.0	39.3
Nadir CD4, per mm^3	164 (32–253)	159 (75–258)	141 (63–241)
HIV VL	1.6 (1.6–1.6)	1.6 (1.6–2.4)	1.6 (1.6–1.75)
VL <40 copies/mL	78.9	68.3	65.5

LL, NL, and HL groups correspond to patients with Ctrough-TDF <40, between 40 and 90, and >90 ng/mL, respectively.
*$P < 0.017$ and †$P < 0.001$ between groups.
CDC, Centers for Disease Control and Prevention; VL, viral load.

Changes in Estimated Glomerular Function Rate

At the time of TDF introduction, BL-GFR values estimated by means of the CG formula were <60 mL/min [median: 55.5 mL/min (IQR: 51.5–58.3)] in 3.7% (n = 6) of the patients. Proportion of patients with BL-GFR between 60 and 90 mL/min (median: 78.1 mL/min [IQR: 72.2–83.5]) and >90 mL/min [median: 110.9 mL/min (IQR: 100.3–123.6)] were 29% (n = 47) and 58% (n = 95), respectively. To exclude an inaccurate estimation linked to the GFR formula used, we also evaluated the GFR using MDRD or CKD-EPI formula for each patient. We observed a high variability of GFR values, especially for the lowest range (Fig. 1). The median (IQR) BL-GFR values measured with MDRD equations were 68.7 (62.4–71.9), 87.7 (76.5–96.2), and 106.8 (96.7–121.5) mL/min in LL, NL, and HL groups, respectively. Corresponding values obtained with CKD-EPI were 70.2 (62.2–76.6), 88.7 (82.9–97.8), and 107.2 (101.7–113.6) mL/min.

The evolution of renal parameters between baseline and the time of Ctrough-TDF determination based on CG formula is presented in Table 2. A significant decrease in GFR between baseline and time of Ctrough-TDF determination was observed only in the HL group, which appeared significant ($P < 0.001$) whatever the formula used to assess renal filtration (see **Table, Supplemental Digital Content,** http://links.lww.com/QAI/A377). When assessed according to gender, the delta BL-T1-GFR was more pronounced in women with a significant difference between HL and NL groups [−11.2 (IQR: −18.5 to −3.1) vs. +0.78 (IQR: −6.1 to +15.1) mL/min; $P = 0.009$].

Median levels of phosphoremia at the time of Ctrough-TDF were within the normal range in the 3 groups, but a significant difference was observed between NL and HL groups (Table 2). Overall, 10 patients had phosphoremia levels less than the threshold of 0.78 mmol/L, 3 in the LL group (0.51, 0.68, and 0.77 mmol/L), 1 in the NL group (0.65 mmol/L), and 6 in the HL group (0.33, 0.57, 0.72, 0.73, 0.74, and 0.74 mmol/L).

A multivariate analysis of factors associated with a decrease in GFR was performed at the time of Ctrough-TDF

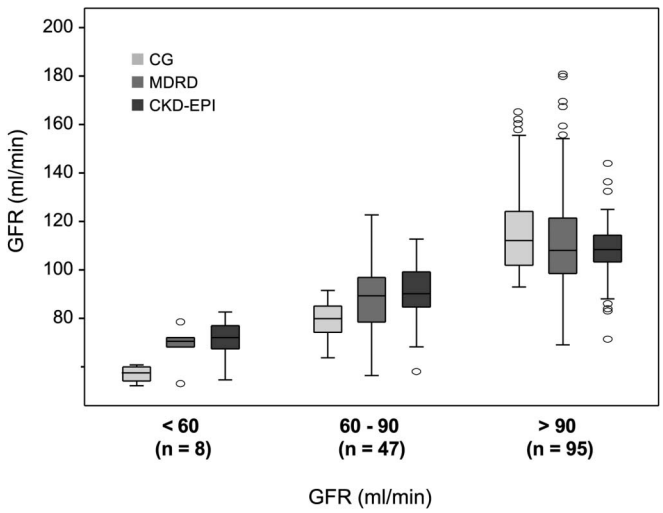

FIGURE 1. Distribution of GFR at the time of TDF introduction determined by CG, MDRD, and CKD-EPI formulae.

TABLE 2. Changes in Renal Parameters Between the Time of TDF Introduction (BL) and Time of TDF Concentration Determination (T1) (Univariate Analysis)

Parameters, Median (IQR)	LL Group, n = 19	NL Group, n = 60	HL Group, n =84	*P*
Time of exposure to TDF, mo	26.1 (3.8–51.1)	19.7 (10.8–50.4)	21.9 (5.1–46.5)	NS
Phosphoremia* at T1, mmol/L	1.03 (0.84–1.34)	1.12 (0.99–1.28)	1.04† (0.89–1.19)	0.028
CG formula				
BL-GFR, mL/min	99.92 (75.2–119.4)	106.9 (92.4–122.2)	93.7 (78.1–111.6)	0.038‡
BL-GFR <60 mL/min, %	5.9	5.7	2.6	NS
T1-GFR, mL/min	103.8 (83.4–126)	104.8 (90.9–124.8)	85.9§ (65.5–103.3)	<0.001
T1-GFR <60 mL/min, %	10.5	6.7	11.9	NS
Delta GFR, mL/min	5.2 (−4.1 to 12.4)	−2.4 (−10.3 to 8.7)	−8.5 (−17.2 to 1.1)	<0.001

LL, NL and HL groups correspond to patients with Ctrough–TDF <40, between 40 and 90, and > 90 ng/mL, respectively.
*Determination in fasting state; normal values between 0.78 and 1.53 mmol/L.
†$P = 0.008$ versus group 2.
‡NS when GFR was assessed by MDRD or CKP-EPI formula.
§$P < 0.001$ between T1 and baseline measurements.
NS, not significant.

determination (Table 3). The final regression model regarding the relation between Ctrough-TDF and a decrease in GFR was stratified by gender. Whatever the GFR formula used, an older age and a higher level of GFR at the time of TDF initiation were significantly associated with a decrease in GFR in both sexes. However, a Ctrough-TDF >90 ng/mL was significantly associated with a decrease in GFR in women but not in men, independently of the time of exposure to TDF. The decrease in GFR was not associated with the presence of diabetes, hypertension, HCV-coinfection, or with the presence of boosted PI or atazanavir (boosted or not) in the antiretroviral regimen.

Longitudinal Assessment of GFR Changes

Data from 98 patients still on the same cART regimen after Ctrough-TDF determination (14, 33, and 51 patients in groups 1, 2, and 3, respectively) were analysed. Women accounted for around one-third of the population. Patient characteristics were similar in the 3 groups, and the median time of exposure to TDF was 38.4 months (IQR: 14.7–71.1).

TABLE 3. Multivariate Analysis of Factors Associated With GFR Changes at the Time of TDF Concentration Determination

	Men		Women	
Variable	Coefficient	*P*	Coefficient	*P*
Age	−0.865	0.001	−1.043	0.03
BMI	1.726	0.028	1.552	0.18
BL-GFR	−0.313	0.007	−0.489	0.01
CTrough-TDF >90 ng/mL	−3.201	0.475	−15.307	0.02
Hypertension	−1.946	0.734	20.657	0.18
Diabetes	−1.346	0.833	14.946	0.22
HCV–PCR+	2.481	0.623	13.274	0.08
PI/r	0.399	0.932	−13.109	0.11
ATV	−4.105	0.364	−6.830	0.37

Data are presented with creatinine clearance estimated according to CG formula. Coefficient was calculated by using a linear regression model adjusting to baseline creatinine clearance values.

Similar results were observed after 12 months of follow-up (10–14 months) for both sexes, with a significantly lower T2-GFR ($P < 0.001$) and a higher decrease in GFR ($P = 0.002$) in patients with a Ctrough-TDF >90 ng/mL, whatever the formula used. Median delta BL-T2-GFR values (CG formula) in LL, NL, and HL groups were −1.69 (IQR: −8.47 to +10.9), −1.28 (IQR: −8.59 to +11.9), and −8.27 (IQR: −20.3 to −0.98) mL/min, respectively ($P = 0.003$). This significant difference was observed whatever the formula used. Median delta BL-T2-GFR in the HL group, estimated by MDRD and CKD-EPI formulae, were −11.8 mL/min (IQR: −25.5 to −1.45, $P < 0.001$ vs. other groups) and −7.40 mL/min (IQR: −16.9 to −2.15, $P < 0.001$ vs. other groups), respectively. Furthermore, the proportion of patients with a decrease in GFR > −10 mL/min was significantly higher in the HL group, whatever the formula used [17% in NL group (whatever the formula used) vs. 44% (CG), $P = 0.017$; 56% (MDRD), $P < 0.001$; 46% (CKD-EPI), $P < 0.001$ in the HL group].

DISCUSSION

This retrospective study including HIV-infected patients followed-up in a French clinical unit showed that high-plasma Ctrough-TDF (>90 ng/mL) may be expected in half of the patients receiving a TDF-containing cART. Low Ctrough-TDF values in the low-level group were all <40 ng/mL, which is our limit of quantification. A possible bias due to the nonadherence to the treatment was unlikely, as indicated by plasma Ctrough values of concomitant PI or NNRTI found to be within the normal range, and also the high percentage of patients with undetectable HIV viral load (<40 copies/mL) in this group (close to 80%).

It is noteworthy that time exposure to TDF was not different in the 3 subgroups defined by TDF concentration. Furthermore, only 5% of the population analysed exhibited GFR <60 mL/min, whatever the method used, which limits misinterpretations due to a possible impact of previous renal failure on TDF concentrations. High Ctrough-TDF was found to be associated with renal dysfunction, which is consistent with data reported by Rodríguez-Nóvoa et al[13] who showed

a dose-dependent effect of TDF plasma concentrations on kidney tubular dysfunction. In this study, the authors proposed a threshold of 160 ng/mL at mid dose (C_{12}) to discriminate a risk of kidney tubular dysfunction. Our results suggest that Ctrough-TDF >90 ng/mL could predict an impact on renal filtration as determined by creatinine clearance. This significant correlation between Ctrough-TDF and the decrease in GFR is in favour of a toxic concentration-dependent effect of TDF on glomerular filtration. In our study, the proportion of patients with a decrease in GFR > −10 mL/min was significantly higher in patients with Ctrough-TDF >90 ng/mL, whatever the formula used. To date, because of the absence of a reported correlation between drug plasma concentration and efficacy, therapeutic drug monitoring is not recommended for NRTI.[1,2] Yet, adverse events resulting from the exposure to plasma NRTI cannot be excluded and monitoring TDF concentration remains questionable because of the impact of the drug on kidney function.[19,20] Our data are consistent with pharmacogenetic[13] and clinical[20] studies supporting such a monitoring to prevent renal toxicity and optimize tolerance profile, especially in patients with a high risk of kidney dysfunction.

The multivariate analysis presented in our study identified higher baseline GFR and older age as independent variables associated with a higher decrease in GFR for men and women. The impact of age was not surprising, as it is known to be associated with chronic renal failure and decreased renal function.[8,12,21–23] No association with hypertension, diabetes, and HCV coinfection, known to be associated with GFR decline,[22] was noted in our study. However, one can postulate that the time since diabetes or hypertension diagnosis (several years) compared with the median duration of TDF exposure (18–26 months) in our study made the assessment of the impact of these comorbidities on TDF-associated renal impairment not feasible from a statistical viewpoint.

Our longitudinal assessment showed a negative impact of high Ctrough-TDF on renal filtration, whatever the sex of the patients. However, the multivariate analysis based on data measured early after TDF introduction (T1-GFR) identified Ctrough-TDF >90 ng/mL as an independent predictive factor of renal impairment in women but not in men. These data suggest an earlier and/or greater susceptibility of women regarding renal toxicity induced by high Ctrough-TDF. In a cohort of HIV patients receiving TDF or not, Goicoechea et al[12] found no association between steady state TDF plasma Cmax and Ctrough and change in GFR over time (24 and 48 weeks), which was ascribed to a poor correlation between TDF plasma levels and renal cell toxicity. However, the cohort included >80% of men and, given the influence of female gender shown in our study, one cannot exclude that an impact of TDF concentrations on renal filtration in women may have been hidden. Furthermore, the authors reported that baseline GFR was lower in women than in men, which could further limit the interpretation and reinforce the hypothesis of a masked effect in women. In a recent study performed in 2 American military clinics, female gender was shown to be significantly associated with a reduction of GFR in HIV-infected patients using TDF, which supports a possible increased susceptibility of women regarding TDF-induced renal dysfunction.[24]

A recent meta-analysis of prospective studies suggests that the significant loss of renal function induced by TDF use may only have a modest clinical impact.[25] On the other hand, long-term retrospective studies assessing HIV patients in "real life" showed worsening renal function and higher risks of proximal tubular dysfunction in HIV patients receiving TDF, which could significantly increase the probability of treatment discontinuation.[8,14] Furthermore, the effect of TDF on renal impairment is expected to be enhanced in patients with preexisting renal impairment, which is observed in 4%–17% of HIV patients,[22] and when TDF is used in association with a PI/r.[3,11,12] In this study, Ctrough-TDF was not significantly increased in patients receiving a PI/r regimen as already reported.[12] However, >70% of the patients had received a PI-based regimen, which could have biased the comparison with patients receiving an NNRTI.

The various formulae used to estimate GFR showed similar results in terms of changes between baseline and both the time of Ctrough-TDF measurement and 12 months later, despite a relative variability of baseline values, especially in the group of patients with the lowest rates of renal filtration. To date, none of the formulae available for the estimation of GFR is validated. Although a similarity of results has been previously reported in HIV-1–infected patients when using CG or MDRD formulae,[22] differences in patients with GFR values between 60 and 90 mL/min have been reported.[26] Studies to validate the most accurate equation for estimating GFR in HIV-infected patients for creatinine clearance calculation remain to be performed.

The main limitation of our study is that it was a retrospective and nonrandomized study, which provides fruitful information in a "real life" setting but was not designed to explore the causality of the relation observed. One the other hand, although the results of several measurements performed in the same patients support a good reproducibility of TDF levels, only one measurement was available for most of the patients over the analysis period. Furthermore, the population was characterized by a large variability in the duration of TDF use, a possible bias that seems, however, limited by the absence of association between Ctrough TDF and the duration of exposure.

In conclusion, this study shows that plasma Ctrough-TDF above a threshold of 90 ng/mL is associated with a decrease in glomerular function and that age and female gender are independent factors associated with an increased risk of renal impairment in HIV-patients receiving a TDF-containing regimen. The significant correlation between Ctrough-TDF and the decrease in GFR highlights a toxic concentration-dependent effect of TDF on glomerular filtration and supports previous studies reporting a tubular nephropathy in patients on a TDF-based regimen. The high prevalence of patients with Ctrough-TDF >90 ng/mL reported in this study emphasizes the interest of therapeutic drug monitoring for TDF, especially in women and older patients. Because TDF-based regimens are widely used in treatment-naive patients or in case of resistance or intolerance to older NRTIs, assessing plasma Ctrough-TDF may be useful to

prevent the risk of renal dysfunction. Therefore, the impact of a dose reduction of TDF according to the residual concentration has to be evaluated. While a dose reduction is currently recommended only when GFR is <50 mL/min, the choice of alternative NRTI-based regimens over dose-adjusted TDF in this setting should be discussed to make sure that antiretroviral efficacy is maintained. Further prospective studies are required to investigate the interest of a dose-adjustment strategy in patients with a higher risk of developing renal impairment.

ACKNOWLEDGMENTS

The authors wish to thank Hervé Bismut for editorial assistance. They are grateful to the patients who trusted them and accepted to belong to their cohort.

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