

ORIGINAL RESEARCH

Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study

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Objectives

Despite the recent publication of case reports describing various manifestations of tenofovir-related nephrotoxicity, data regarding the incidence of and risk factors for this adverse effect are currently lacking.

Methods

A retrospective cohort study of patients from four centres in Toronto, Canada, enrolled in the tenofovir expanded access programme with a minimum of 3 months follow up, was carried out.

Results

A total of 172 patients receiving tenofovir disoproxil fumarate (TDF) for a median of 16 months (range 3–25 months) were included in the study. Seven (4%) patients developed grade 1 (> 44 µmol/L from baseline) increases in serum creatinine (SCr) during follow up; no patient developed grade 2 or higher nephrotoxicity. Fifteen (8.7%) patients had an increase in SCr of greater than 1.5 times baseline values during follow up. Four (2.3%) patients discontinued TDF because of an increase in SCr and/or abnormal urinalysis. Of 62 patients with a urinalysis, grade 1 or higher proteinuria (< 3 g/L) was observed in 27 (43%) patients. Only baseline SCr [odds ratio (OR) = 0.51 per 10 µmol/L increase; $P = 0.0005$] and baseline creatinine clearance (1.26 per 10 mL/min increase; $P = 0.01$) were significantly associated with ever having a 1.5-fold increase in serum creatinine. Twenty-eight (16%) and 11 (6%) patients developed grade 1 (serum phosphorus ≤ 0.71 mmol/L) and grade 2 (serum phosphorus ≤ 0.61 mmol/L) hypophosphataemia during follow-up, respectively.

Conclusions

Although slight increases in SCr did occur after starting TDF, clinically significant nephrotoxicity was rare. The clinical significance of TDF-related hypophosphataemia and proteinuria requires further study.

Keywords: adverse effects, anti-HIV agents, creatinine, kidney, tenofovir

Received: 14 September 2004, accepted 5 January 2005

Introduction

Tenofovir disoproxil fumarate (TDF) is the only nucleotide analogue currently available for the management of HIV infection. The efficacy of TDF was initially established in two clinical trials with antiretroviral (ARV)-experienced patients, in which the addition of TDF to stable background therapy resulted in a significant decrease in viral load relative to placebo, with a similar incidence of adverse

effects [1]. In addition, study GS-903 established TDF as a comparable alternative to stavudine when used in combination with lamivudine and efavirenz in ARV-naive patients, while eliciting less mitochondrial and metabolic toxicity [2]. The convenience of once-daily administration coupled with a favourable toxicity profile has rendered TDF a welcome addition to the ARV arsenal. Importantly, unlike structurally related nucleotide analogues such as didanosine and zalcitabine, clinically significant nephrotoxicity did not emerge as a treatment-limiting adverse effect of TDF in the clinical trials. Furthermore, the renal safety profile of TDF was similar to that of stavudine over 144 weeks of follow-up in study GS-903 [2].

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However, post-marketing experience with TDF has raised the possibility that nephrotoxicity may be an uncommon but important adverse effect of this agent. Several case reports describing nephrotoxicity attributable to TDF have been published, with manifestations of Fanconi syndrome, nephrogenic diabetes insipidus and acute renal failure being reported [3–14]. To better describe the incidence of and potential risk factors for TDF-associated nephrotoxicity in routine clinical care, we performed a retrospective review of patients enrolled in the TDF Expanded Access Programme (EAP) in Toronto, Canada.

Methods

Study population and study design

We conducted a retrospective cohort study of HIV-infected adults who were enrolled in the TDF EAP in Toronto from January 2002 to December 2003. The participating sites included a primary care clinic specializing in the provision of HIV-related care, a hospital-affiliated inner-city family practice clinic and two hospital-based HIV specialty clinics. All patients enrolled in the EAP were identified by the individual site study co-ordinator and were considered for inclusion in the study. Consent from each patient and ethics approval at each institution were obtained prior to analysis. Patients were eligible for inclusion in the study if they had been receiving TDF for a minimum of 3 months and had baseline weight, baseline serum creatinine (SCr) and baseline serum phosphorus (PO₄) levels available. Baseline creatinine clearance was calculated using the Cockcroft–Gault equation [15].

Data collection

A standard data collection form was used to record data from each site. Charts of eligible patients were reviewed for the extraction of baseline demographic data and baseline and follow-up laboratory data. Demographic variables included date of birth, gender, risk factor for and duration of HIV infection, co-infection with either hepatitis B or C, concurrent medical conditions that may predispose to nephrotoxicity (e.g. diabetes), concurrent nephrotoxic medications (e.g. nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole and angiotensin converting enzyme (ACE) inhibitors), and ARV treatment history. The dose of ARV agents co-administered with TDF was also documented. Laboratory parameters included all follow-up SCr and PO₄ results, which were obtained at the discretion of the treating physician. The results of baseline and follow-up urinalysis, 24-h urine collection, renal ultrasound or renal biopsy were also recorded if performed.

Extracted data were entered into an Access database (Microsoft Corp., Redmond, WA).

Study endpoint definitions

The primary endpoints of the study included a grade 1 ($\geq 44 \mu\text{mol/L}$) or higher increase in SCr, a greater than 1.5-fold increase in SCr from baseline and a grade 1 ($\leq 0.71 \text{ mmol/L}$) or higher hypophosphataemia. Changes in SCr and serum PO₄ levels from baseline were also assessed. Secondary endpoints included the rates of anomalies identified on urinalysis. Specific outcomes of interest were grade 1 ($< 3 \text{ g/L}$) or higher proteinuria and grade 3 ($> 28 \text{ mmol/L}$) or higher glucosuria with a normal plasma glucose.

Statistical analysis

Baseline characteristics were summarized with medians and interquartile ranges (IQRs) or proportions. Changes over time in SCr and PO₄ levels were summarized with medians and IQRs at various follow-up times. Wilcoxon signed rank tests were used to determine whether changes over time in PO₄ and SCr levels were significantly different from zero. Logistic regression models were used to determine odds ratios (ORs) associated with experiencing a 1.5-fold increase in serum creatinine during the study period from the baseline level. All statistical analyses were performed using SAS version 8.2 statistical software (SAS Institute, Cary, NC).

Results

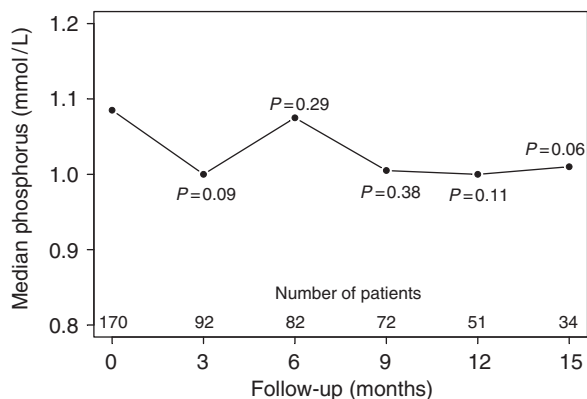
Patient characteristics

Three hundred and nine patients were enrolled in the TDF EAP at the three sites. A total of 137 patients did not meet the inclusion criteria and were therefore excluded from the study. Reasons for exclusion included the following: received TDF for less than 3 months ($n = 69$); never started TDF ($n = 46$); insufficient baseline information ($n = 11$); and patient lost to follow-up ($n = 11$). One hundred and seventy-two patients were therefore eligible for inclusion in the analysis. Patients received TDF for a median of 16 months (range 3–25 months). Baseline characteristics of the cohort are described in Table 1.

At initiation of TDF therapy, all 172 patients were ARV treatment-experienced. Of these patients, 35 (20.3%) switched only one agent to TDF for the purposes of treatment simplification and/or amelioration of a specific adverse effect. The majority of these changes occurred in the context of an undetectable ($< 50 \text{ copies/mL}$) viral load.

Table 1 Demographic characteristics

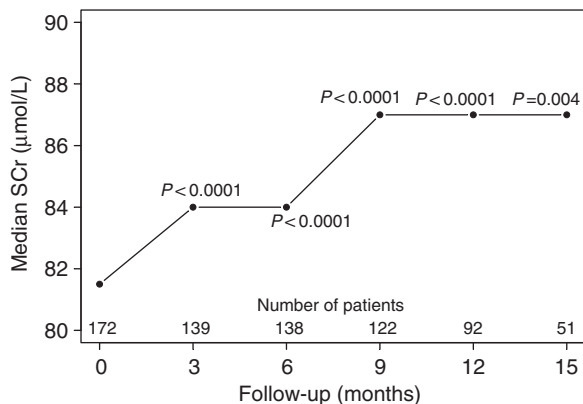
Characteristic	
Age (years)*	46 (41–52)
Male [n (%)]	159 (93%)
Duration of HIV infection (years)	12 (9–15)
Baseline CD4 count (cells/ μL)*	260 (110–450)
Baseline viral load (\log_{10} copies/mL)*	3.74 (1.69–4.75)
Baseline serum creatinine (mmol/L)*	81.5 (71.0–91.5)
Baseline creatinine clearance (mL/min)*	101 (85–120)
Baseline phosphorus (mmol/L)*	1.085 (0.91–1.21)
Number of previous antiretrovirals*	8 (6–10)
Time on antiretrovirals (years)*	9.0 (7.2–12.0)

*Median (interquartile range). $n = 172$.**Fig. 1** Median phosphorus level by month of follow-up.

Five (2.9%) and 132 (76.7%) patients had TDF alone and TDF with at least one other ARV drug added to their regimen, respectively. A total of 54 (31.4%) patients had an undetectable viral load at the time of TDF initiation. TDF was prescribed in combination with a protease inhibitor (PI)-based (including single or boosted PI), dual PI-based, nonnucleoside reverse transcriptase inhibitor (NNRTI)-based and other (e.g. PI/NNRTI) regimen in 57 (33.1%), 30 (17.4%), 29 (16.9%) and 56 (32.6%) patients, respectively. One hundred and fourteen (66.3%) patients in the cohort received TDF in combination with lopinavir/ritonavir.

Incidence of nephrotoxicity

Median changes in SCr and serum PO_4 by duration of follow-up are summarized in Figs 1 and 2. Although statistically significant increases in SCr relative to baseline were observed at 3–15 months of follow-up, changes at each time point were of small magnitude and are unlikely to be clinically relevant. Also, increases in SCr appeared to plateau over time. Similarly, median decreases in serum phosphorus were small and probably clinically negligible.

**Fig. 2** Median serum creatinine (SCr) level by month of follow-up.

During follow-up, seven patients (4%) developed grade 1 increases in SCr at a median of 334 days (212–665 days) following the initiation of TDF; no patient developed grade 2 or higher nephrotoxicity.

Fifteen patients (8.7%) had a 1.5-fold or greater increase in SCr relative to baseline at a median of 244 days following the initiation of TDF (range 120–669 days), four of whom had grade 1 levels of SCr. The median SCr at baseline among patients who had a 1.5-fold increase in SCr was significantly lower than that of patients who did not: 62 $\mu\text{mol/L}$ (IQR 49–82 $\mu\text{mol/L}$) vs. 82 $\mu\text{mol/L}$ (IQR 72–92 $\mu\text{mol/L}$) ($P = 0.003$). The median creatinine clearance at baseline among patients with a 1.5-fold increase was significantly higher than that of patients without the increase: 117 mL/min (IQR 98–139 mL/min) vs. 100 mL/min (IQR 85–117 mL/min) ($P = 0.015$). In three of the 15 patients, SCr had returned to baseline values within 6 months of follow-up. Of the remaining patients, three had no further follow-up values and nine had sustained increases in SCr of approximately 1.2–2 times baseline values at 1–9 months following the initial increase to at least 1.5-fold baseline values. Thirteen of the 15 patients were male.

Four patients (2.3%) discontinued TDF at a median of 16 months (10–18 months) of follow-up because of nephrotoxicity. Three of the patients developed a constellation of findings consistent with a diagnosis of Fanconi syndrome, including proteinuria, hypophosphataemia, hypouricaemia and glucosuria with a normal plasma glucose. In two of these cases, findings on urinalysis and SCr normalized following the discontinuation of TDF. The third patient was lost to follow-up once TDF was discontinued. The remaining patient discontinued TDF because of a progressive increase in SCr to 122 $\mu\text{mol/L}$ (baseline of 86 $\mu\text{mol/L}$) 18 months following the initiation of TDF as well as a decrease in serum PO_4 from 0.85 to 0.57 mmol/L

Table 2 Univariate logistic regression models with a 1.5-fold increase in serum creatinine from baseline (ever) as the outcome

	Odds ratio (95% CI)	P-value
Age (per 10 years)	1.15 (0.62–2.14)	0.65
Gender	2.25 (0.44–11.36)	0.33
Time on antiretrovirals (years)	0.92 (0.78–1.08)	0.29
Number of previous antiretrovirals	0.95 (0.78–1.16)	0.62
Time on tenofovir (months)	1.06 (0.94–1.19)	0.36
Baseline CD4 (per 100 cells/ μ L)	0.95 (0.77–1.18)	0.66
Baseline viral load (\log_{10} copies/mL)	1.0005 (0.87–1.14)	0.99
Baseline SCr (per 10 μ mol/L)	0.51 (0.35–0.75)	0.0005
Baseline weight (per kg)	0.97 (0.92–1.02)	0.23
Concomitant disease	1.26 (0.40–3.84)	0.69
Nephrotoxic drug	1.72 (0.57–5.32)	0.34
LPV/r or IDV at baseline	3.01 (0.66–13.97)	0.16
Baseline CrCl (per 10 mL/min)	1.26 (1.05–1.51)	0.01

CI, confidence interval; SCr, serum creatinine; LPV/r, lopinavir/ritonavir; IDV, indinavir; CrCl, creatinine clearance.

within the same follow-up period. Grade 1 proteinuria was also evident on urinalysis. Abnormal findings resolved with the discontinuation of TDF. Although all four patients had an increase in SCr relative to baseline, none reached a grade 1 increase. Of the four patients, three were receiving concomitant lopinavir/ritonavir, and three were receiving at least one additional medication with nephrotoxic potential (i.e. ramipril, trimethoprim-sulfamethoxazole, acyclovir, indapamide or celecoxib).

In total, 67 patients underwent a urinalysis during the study period. Grade 1 and 2 proteinuria was observed in 25 (37.3%) and two (3%) of these patients, respectively. Five (7.5%) patients had grade 3 or higher glucosuria. Only 11 patients had a baseline urinalysis performed within 1 year of initiating TDF available for comparison. Of these 11 patients, five had baseline grade 1 proteinuria and six had normal baseline urinalyses. Following the initiation of TDF, the degree of proteinuria worsened in only one of five patients with pre-existing abnormal urinalysis (grade 1 to grade 2). This patient also developed grade 3 glucosuria. Of the six patients with no abnormalities in baseline urinalysis, grade 1 or higher proteinuria developed in all patients, while only one patient developed grade 3 glucosuria.

Incidence of hypophosphataemia

Twenty-eight (16%) and 11 (6%) patients developed grade 1 and grade 2 hypophosphataemia during follow-up, respectively. Hypophosphataemia tended to be transient and never reached grade 3 or higher at any point during follow-up.

Risk factors of a 1.5-fold increase in serum creatinine

In univariate analysis, only baseline SCr (OR = 0.51 per 10 μ mol/L increase; $P = 0.0005$) and baseline creatinine

clearance (OR = 1.26 per 10 mL/min increase; $P = 0.01$) were associated with the development of a 1.5-fold or higher increase in serum SCr relative to baseline. No significant relationship was identified with other potential confounding variables, including the receipt of potentially nephrotoxic agents, duration of TDF exposure or the concomitant receipt of either indinavir or lopinavir/ritonavir with TDF (Table 2).

Discussion

The propensity to cause nephrotoxicity is a well-known trait of nucleotide analogues. The mechanism underlying this complication is thought to be related to their active cellular uptake by the human renal organic anion transporter-1 (hOAT-1) which is expressed on the cells of the proximal tubule [16]. Although TDF is similar to other nucleotide analogues in its affinity for hOAT-1, *in vitro* data suggest that TDF is substantially less toxic to renal proximal tubule epithelial cells than cidofovir [16,17]. Also, no significant changes in mitochondrial DNA levels were observed in renal proximal tubule epithelial cells exposed to TDF concentrations ranging from 3 to 300 μ M [18]. Furthermore, evidence of renal toxicity in animals was observed at TDF exposures 2–20 times greater than those used in humans [19]. Taken together, these findings suggest that TDF-mediated nephrotoxicity at therapeutic doses would be unlikely, a conclusion corroborated by the weight of clinical trial data published thus far. In two separate clinical trials with ARV-experienced patients, no patient developed grade 2 or higher changes in SCr during a mean of 58 weeks of follow-up [1]. Furthermore, the renal safety profile of TDF was similar to that of stavudine during 144 weeks of follow up in ARV-naïve patients, with <1% of patients per group developing grade 2 or higher nephrotoxicity [2]. Finally, a retrospective review of patients receiving TDF identified 8.4% of patients as having attained a greater than 1.5-fold increase in SCr within 6 months of starting therapy, which is very similar to the incidence in our cohort [20].

The results of our study lend further support to the conclusion that TDF is a generally well-tolerated ARV agent from a renal standpoint. Only 15 patients had at least a 1.5-fold or greater increase in SCr during follow up, four of whom reached grade 1 nephrotoxicity. In addition, only four patients discontinued TDF because of suspected nephrotoxicity, three of whom appeared to have developed features consistent with Fanconi syndrome. Although increases in SCr were sometimes transient, sustained elevations from baseline remained in most patients for whom additional data were available. Longer term follow up will be necessary to determine whether a downward

trend towards normal values would eventually occur or whether some degree of renal impairment persists in patients with TDF-associated nephrotoxicity. The possibility of irreversible changes in renal function is supported by evidence from case reports describing only a partial return towards baseline for SCr and findings of fibrotic lesions on kidney biopsy. However, these data are clearly limited by the anecdotal nature of case reports and the limited or unknown duration of follow up once TDF was discontinued.

Risk factors for TDF-mediated nephrotoxicity remain poorly defined. Because the risk of nephrotoxicity with TDF may be dose-related, the receipt of concomitant agents that increase TDF levels may inadvertently increase the risk of eliciting this adverse effect. The combination of lopinavir/ritonavir and TDF has been documented to increase TDF levels by approximately 30%, and may augment the potential for nephrotoxicity further by inhibiting the multidrug resistance protein (MRP)2-mediated efflux of TDF from the proximal tubule, thereby facilitating intracellular drug accumulation [21,22]. Virtually all cases of nephrotoxicity published thus far have been in patients who have been receiving TDF with either lopinavir/ritonavir or ritonavir in combination with another PI, lending some support to this theoretical association. However, in our univariate analysis, concurrent receipt of lopinavir/ritonavir was not significantly associated with a greater than 1.5-fold increase in SCr, a finding supported by other investigators [20,23]. Instead, only baseline SCr and creatinine clearance were significantly associated with nephrotoxicity in our study. We are unclear, however, why the results would suggest that patients with seemingly healthier kidneys at baseline were more predisposed to developing this complication. It is possible that, for patients with high starting levels of SCr, it is more difficult to attain our predefined endpoint of a 1.5-fold or higher increase from baseline. In the only other study to examine an association between baseline SCr and nephrotoxicity (in this case, time to onset of elevated SCr), a statistically significant association could not be demonstrated by univariate analysis [20]. However, in a subanalysis of this study, the OR for renal toxicity was 1.19 per 1 mL/min decrease in glomerular filtration rate as calculated by the Levey modification of diet in renal disease (MDRD) formula [24]. These results contradict those of our study, in that the OR for nephrotoxicity was 1.26 per 10 mL/min increase in creatinine clearance. It is unclear if the differences between the two cohorts are a result solely to the method used to estimate glomerular filtration rate, or if other factors are involved.

Hypophosphataemia in our study was generally a transient finding, and resulted in the discontinuation of

TDF only as part of a larger spectrum of disturbances consistent with Fanconi syndrome. Similar conclusions regarding anomalies in serum phosphorus level were noted in studies of ARV-experienced patients. More recently, an analysis of 259 ambulatory HIV-infected patients did not identify TDF as being significantly associated with hypophosphataemia on univariate analysis, despite a higher frequency of this finding than noted in previous studies (30.7% of patients of receiving TDF). Instead, only cumulative time on combination ARV therapy and current use of lopinavir/ritonavir were significantly associated with hypophosphataemia in multivariate analysis [25]. The significance and aetiology of hypophosphataemia remain unclear at present. Given the often transient nature of hypophosphataemia, patients with asymptomatic changes in serum phosphorus should have these levels reassessed periodically before withdrawing therapy with TDF. In the absence of clinical findings, continuing TDF with or without phosphorus supplementation would appear to be a reasonable course, assuming that alternative causes of hypophosphataemia and renal dysfunction are ruled out.

Abnormal findings on urinalysis were common in our patients, with grade 1 or 2 proteinuria being noted in 27% of patients with a follow-up urinalysis performed. The significance of these findings is presently unclear, and interpretation is limited by the lack of baseline and follow-up urinalyses. In addition, grade 1 or higher proteinuria was noted in 18% and 23% of ARV-naive patients receiving tenofovir or stavudine, respectively, in study GS-903 [2]. Also, 3% of patients in each group had grade 3 or higher glucosuria. Thus, it is unclear whether proteinuria or glucosuria arises solely in the context of TDF, or whether other factors are important in the development of these abnormalities. Further study is needed to elucidate the significance of these findings.

Our study has several important limitations, including its retrospective nature and lack of a control group. In addition, the small number of events documented may have resulted in insufficient power to identify significant associations between baseline variables and the occurrence of nephrotoxicity. Also, our patients may have been at low risk for nephrotoxicity because of their well-preserved renal function at baseline. Still, although some cases of TDF-associated nephrotoxicity have occurred in the context of underlying kidney dysfunction, other authors have reported this side effect in patients with normal renal function prior to the initiation of TDF [4,5,14]. Also, it is difficult to fully account for the surprising association amongst baseline SCr, creatinine clearance and the development of nephrotoxicity. It is also possible that, by restricting the analysis to patients who had been on TDF for a minimum of 3 months, cases of nephrotoxicity with an

earlier onset would have been missed and the safety of TDF from a renal perspective would be overestimated. However, the majority of cases reported thus far suggest that this adverse effect is not an early complication of TDF therapy. In addition, a small cohort study did not find any changes in SCr during the first 3 months of TDF therapy [26]. It is, therefore, unlikely that we missed a large number of cases. Finally, the cohort was comprised largely of men, making it very difficult to apply similar conclusions regarding the renal safety of TDF to HIV-positive women. Still, the study provides some reassurance that, in most patients who receive therapy with a TDF-based regimen, the likelihood of clinically significant nephrotoxicity is relatively low.

In summary, although slight increases in SCr did occur after starting TDF, clinically significant nephrotoxicity was uncommon. However, because small increases in SCr may translate into large changes in glomerular filtration rate in patients with normal baseline renal function, our results suggest that tenofovir may not be completely free of nephrotoxic potential. Further research is necessary to determine the significance and aetiology of hypophosphataemia and proteinuria related to TDF.

Acknowledgements

We would like to thank the patients and staff at the participating sites for their contribution to this work.

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