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Renal function with use of a tenofovir-containing initial antiretroviral regimen

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Abstract

Objectives—To determine whether tenofovir disoproxil fumarate (TDF) is associated with renal dysfunction when used as part of an initial antiretroviral regimen and to assess the effect of ritonavir-boosted protease inhibitor (PI/r) coadministration on renal function in TDF-treated patients.

Design—Analysis from a prospective observational cohort.

Methods—We compared all antiretroviral-naive patients with an estimated glomerular filtration rate (eGFR) of more than 50 ml/min per 1.73 m^2 (modification of diet in renal disease equation) who initiated either TDF (n = 201) or any alternative nucleoside reverse transcriptase inhibitor (NRTI) (n = 231) after 1 January 2002.

Results—Patients taking both TDF and NRTIs experienced an initial decline in eGFR during the first 180 days of therapy, but eGFR stabilized between 180 and 720 days. There was no difference between TDF and NRTI use in 25 or 50% decline in eGFR at 1 or 2 years or in change in eGFR at 6, 12, or 24 months. Those taking TDF and a PI/r had a greater median decline in eGFR than those taking TDF and a non-NRTI at 6 months (P = 0.01), with trends at 12 (P = 0.08) and 24 months (P = 0.08). There was no difference in median GFR decline between those on an NRTI and PI/r vs. an NRTI and non-NRTI.

Conclusion—Our data are consistent with results of clinical trials, which have shown no evidence of renal toxicity when TDF is used as part of an initial regimen. Our results support the use of TDF as a component of the initial antiretroviral regimen, and suggest that the eGFR should be monitored more closely when TDF is used with a PI/r.

Keywords

antiretroviral; kidney; nephrotoxicity; nucleoside analog reverse transcriptase inhibitor; protease inhibitor; renal; tenofovir

Introduction

The nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF) is excreted renally via a combination of glomerular filtration and active tubular secretion. TDF has an excellent renal safety profile in clinical trials in antiretroviral-naive individuals [1–6]. However, there have been case reports of renal toxicity, including acute tubular necrosis [7] and Fanconi syndrome [8–10]. Some observational studies [11,12] have found evidence of a mild decrease in kidney function in TDF-treated patients. In a previous study [13] from the

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Johns Hopkins HIV Database, we found a significantly greater decline in estimated glomerular filtration rate (eGFR) in TDF-treated patients compared with those taking nucleoside analog reverse transcriptase inhibitors (NRTIs) without TDF, although the decline in eGFR was mild, and there was no difference between groups in rates of discontinuation because of renal insufficiency. A subsequent analysis [14] suggested that the decline in kidney function, which was observed in both TDF and NRTI-treated patients, was most pronounced in the first 6 months but was not progressive with continued dosing.

In a prior analysis [13] from the Johns Hopkins database, the use of ritonavir-boosted protease inhibitors (PI/r) was not associated with renal dysfunction by multivariate analysis. However, there are conflicting data on whether the use of PI/r-based regimens increases the risk of TDF-mediated renal toxicity. Some PI/r-containing regimens can increase tenofovir exposure by 20–30% [15,16], and it has been suggested that the use of TDF in PI/r-based regimens could increase the risk of nephrotoxicity [7]. Goicoechea and colleagues [17] found that patients treated with PI/r-based regimens had a significantly greater decline in renal function than those taking TDF with non-NRTIs (NNRTIs) or non-TDF-based regimens. In contrast, data from the HIV Outpatient Study (HOPS) found no such difference [18]. We wished to determine whether TDF is associated with renal dysfunction when part of an initial antiretroviral regimen in antiretroviral-naive patients in clinical practice, and to assess the effect of PI/r coadministration on renal function in TDF-treated patients.

Methods

The study sample consisted of HIV-infected patients receiving care in an urban HIV primary care clinic in Baltimore, Maryland who were antiretroviral naive, had an eGFR of more than 50 ml/min per 1.73 m^2, and who initiated an antiretroviral regimen containing TDF or any NRTI after 1 January 2002. The methods of data collection for this observational longitudinal cohort have been described elsewhere [19]. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation [20]. Baseline eGFR was defined as the average of the two eGFRs obtained closest to and preceding the start of treatment by no more than 180 days. Change in eGFR was calculated from average of maximum serum creatinine measurements for each patient and the next creatinine obtained. If there was no on-treatment creatinine measurement after the maximum creatinine, then the maximum creatinine and the creatinine immediately prior to maximum were averaged. Two values were used to minimize regression to the mean.

We calculated change in eGFR in two ways. First, we calculated the time to a 25 and 50% decline in GFR from the baseline level (confirmed by two measures of creatinine) to a maximum of 2 years after starting TDF or an NRTI. We used right-censored Kaplan–Meier methods to determine time to eGFR decline. Censoring occurred at discontinuation of the baseline therapy, leaving care, or at 2 years. The log-rank test was used to determine statistical significance. Multivariate analyses were performed using Cox proportional hazards regression to assess therapy (TDF vs. alternative NRTI) and other demographic and clinical factors associated with eGFR decline. Second, we analyzed the absolute difference in eGFR from baseline by 6-month intervals after the start of therapy. For these analyses, the eGFR obtained closest in time to the interval threshold was used. If patients remained on their initial therapy and did not have eGFR measured in that interval, then the last measured value was carried forward.

Results

There were no significant differences between the TDF and NRTI groups in several demographic and clinical variables (Table 1). The majority of patients in the NRTI group

were taking zidovudine (57%); abacavir was used by 37%, stavudine by 37%, and didanosine by 6%. Patients taking both TDF and NRTIs experienced an initial decline in eGFR during the first 180 days of therapy, but eGFR stabilized between 180 and 720 days. There was no difference by TDF vs. NRTI use in 25 or 50% decline in renal function by 2 years of follow-up (Fig. 1) and no significant difference between TDF and NRTI use in the change in eGFR from baseline value at 6, 12, and 24 months (Fig. 2).

By multivariate analysis, there was no difference between the TDF and NRTI groups in 25% ($P = 0.39$) or 50% decline ($P = 0.56$) adjusting for age, race, baseline eGFR, and CD4 cell count, use of a PI/r vs. NNRTI-based regimen, concomitant diabetes, or hypertension (Table 2). Factors associated with greater than 25% decline in eGFR included age more than 45 years [hazard ratio 2.31, 95% confidence interval (CI) 1.44–3.69], baseline CD4 cell count less than 200 cells/μl (HR 2.66, 95% CI 1.65–4.29), hypertension (HR 1.56, 95% CI 1.00–2.45), and use of a PI/r (HR 2.14, 95% CI 1.37–3.34). Race, diabetes, and TDF vs. NRTI use were not associated with decline in eGFR after adjusting for the former variables.

When analyzed by TDF vs. NRTI use, the group taking TDF and a PI/r had a greater decline in eGFR than those taking TDF and an NNRTI at 6 months ($P = 0.01$), with a trend observed at 12 months ($P = 0.08$) and 24 months ($P = 0.08$) (Fig. 3). In contrast, there were no significant differences between those taking NRTIs and a PI/r compared with those taking NRTIs and an NNRTI ($P = 0.92$, 0.81, and 0.85, respectively).

Discussion

We observed a modest initial decline in eGFR among antiretroviral-naive patients starting both TDF and alternative NRTIs as part of their initial antiretroviral regimen, with no significant difference between the two groups. These results emphasize the importance of always including a control group that receives an alternative NRTI when studying the effect of TDF on renal function, as the decline in renal function could have otherwise been attributed to TDF.

In contrast to our previous analyses, we found a significantly greater decline in eGFR between patients who took TDF with a PI/r compared with those who took TDF with an NNRTI. Data from other cohorts have been conflicting. No difference was observed in the HOPS, which included patients taking TDF both for initial and subsequent therapy [18]. In contrast, other studies or reports [7,17] have found evidence of a greater risk of renal toxicity in patients taking TDF with protease inhibitors. A study [17] from the California Collaborative Trials Group, which included both treatment-naive and experienced patients, found significantly greater declines in renal function among patients treated with TDF and a PI/r compared with those treated with TDF and an NNRTI. However, in contrast to the steady decline reported by these investigators, our results showed initial declines over the first 6 months, which subsequently plateaued over the 2-year observation period (Fig. 3).

The mechanism by which coadministration of protease inhibitors might increase the risk of TDF nephrotoxicity remains unclear. Coadministration of some protease inhibitors can increase tenofovir plasma exposure by 20–30% [16]. It has been debated whether this increase in plasma levels is due to a decrease in tenofovir renal clearance [21,22] or an increase in TDF oral absorption [23,24]. HIV drug accumulation in renal proximal tubule cells is determined in part by excretion into the urine by renal transporters [25]. It has been proposed that ritonavir could inhibit the active tubular secretion of tenofovir mediated by the multidrug resistance-associated protein (MRP)-2 transporter, leading to intracellular accumulation of the drug [26]. However, independent laboratories have reported that tenofovir is a substrate for MRP-4, a transporter not inhibited by ritonavir, and not MRP-2

[11,27,28]. Regardless of which mechanism is correct, the lack of progressive decline in renal function seen in our study, together with the lack of significant renal toxicity observed in clinical trials in which TDF was used in PI/r-based regimens [3–5], suggest that this is not a widespread problem.

Consistent with data from randomized clinical trials, our results support the use of tenofovir as part of an initial antiretroviral regimen, whether PI/r or NNRTI-based. Our data also suggest that the GFR should be monitored more closely in older patients, patients with hypertension, patients with baseline CD4 cell counts less than 200 cells/μl, and when a PI/r is used.

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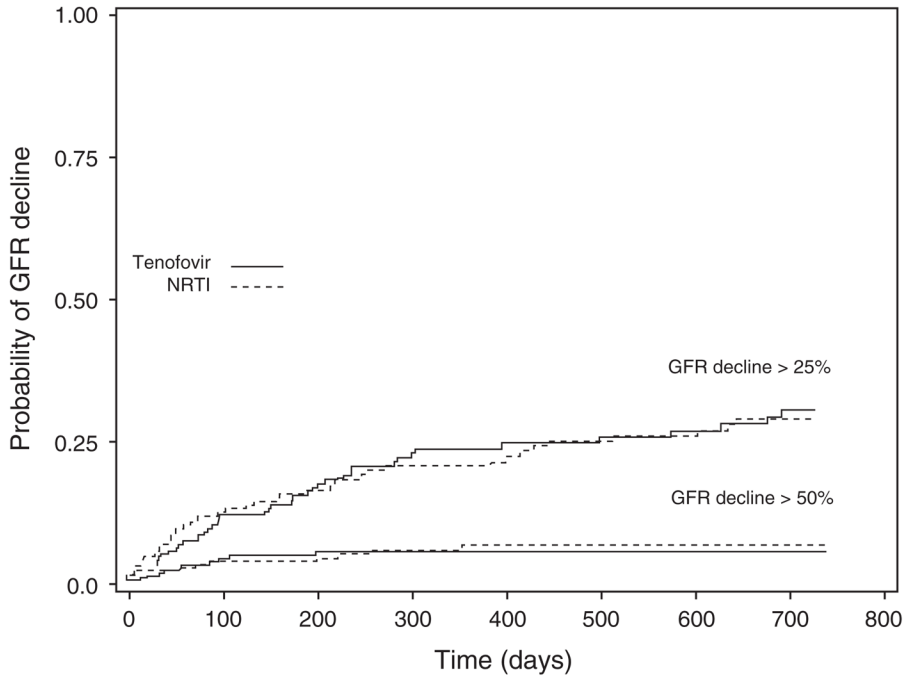

Fig. 1. Kaplan–Meier plots of estimated glomerular filtration rate decline greater than 25% and greater than 50% from baseline value stratified by tenofovir disoproxil fumarate vs. nucleoside reverse transcriptase inhibitor use

There is no significant difference between TDF and NRTI use for a 25% decline ($P = 0.59$) nor for a 50% decline ($P = 0.65$, log-rank test). GFR, glomerular filtration rate; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

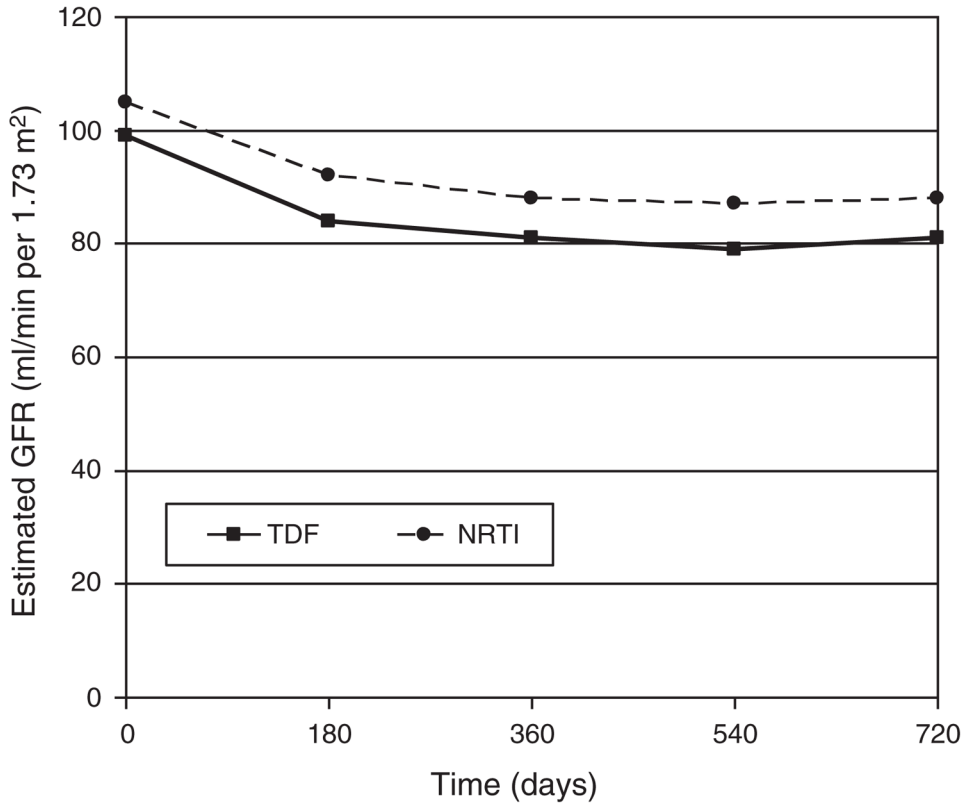

Fig. 2. Plots of the absolute estimated glomerular filtration rate over 2 years from start of therapy by tenofovir disoproxil fumarate vs. nucleoside reverse transcriptase inhibitor use

There is no significant difference between TDF and NRTI use in the median change in eGFR from baseline value at 6 months (TDF, −14; NRTI, −12; $P = 0.26$, median scores test), at 12 months (TDF, −15; NRTI, −14; $P = 0.76$), or at 24 months (TDF, −16; NRTI, −15; $P = 0.76$). All eGFR values are expressed in ml/min per 1.73 m^2. eGFR, estimated glomerular filtration rate; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

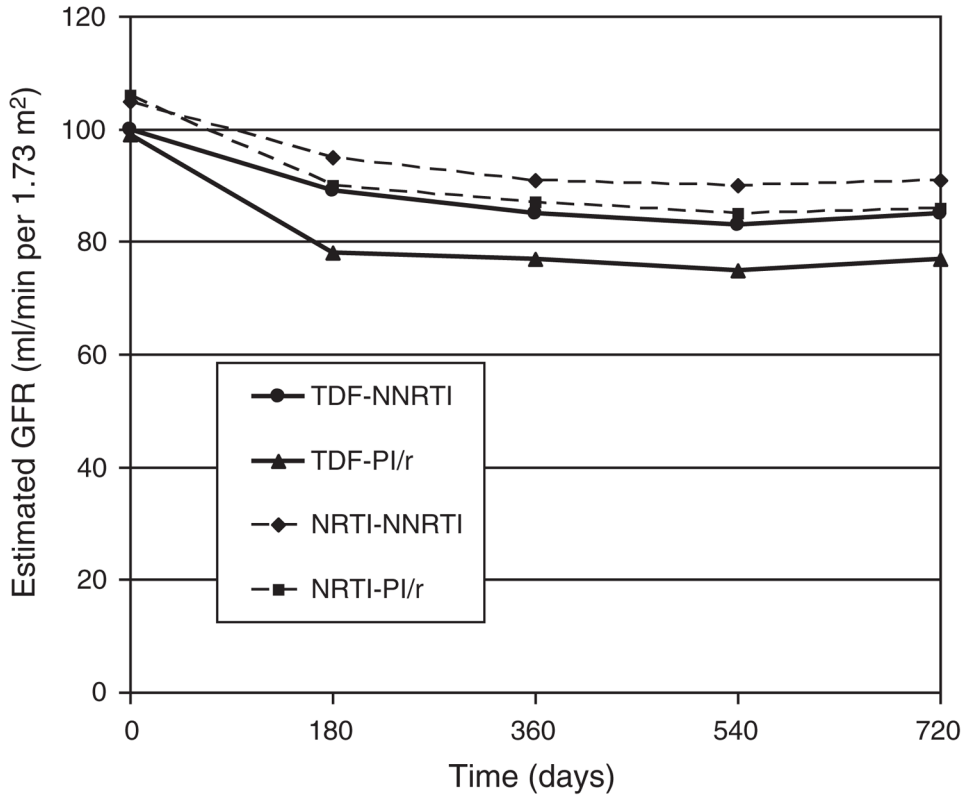

Fig. 3. Plots of the estimated glomerular filtration rate over two years from start of therapy stratified by tenofovir disoproxil fumarate–nucleoside reverse transcriptase inhibitor, tenofovir disoproxil fumarate–ritonavir-boosted protease inhibitor, nucleoside reverse transcriptase inhibitor–nonnucleoside reverse transcriptase inhibitor, and nucleoside reverse transcriptase inhibitor–ritonavir-boosted protease inhibitor

For patients receiving TDF, there is a significant difference between concomitant use of PI/r vs. NNRTI in the median change in eGFR from baseline value at 6 months (PI/r, −18; NNRTI, −10; $P = 0.01$), with a trend at 12 months (PI/r, −18; NNRTI, −13; $P = 0.08$), and at 24 months (PI/r, −18; NNRTI, −13; $P = 0.08$). For patients receiving an NRTI, there was no significant difference between concomitant use of PI/r vs. NNRTI in the median change in eGFR from baseline at 6 months (PI/r, −13; NNRTI, −12; $P = 0.92$), 12 months (PI/r, −16; NNRTI, −14; $P = 0.81$), or 24 months (PI/r, −16; NNRTI, −14; $P = 0.85$). All eGFR values are expressed in ml/min per 1.73 m^2. eGFR, estimated glomerular filtration rate; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.

Table 1

Baseline characteristics of patients who received tenofovir disoproxil fumarate or a nucleoside reverse transcriptase inhibitor.

	TDF (*n* = 201)	NRTI (*n* = 231)	*P*
Time on regimen, days (95% CI)	438 (163–720[a])	410 (102–720[a])	0.27
Baseline eGFR (ml/min per 1.73 m^2)	101	105	0.17
Age (mean years)	40	40	0.94
Race (black)	78%	73%	0.24
Sex (male)	59%	61%	0.77
CD4 cell count, baseline (cells/μl)	246	279	0.80
HIV RNA, baseline (copies/ml)	99 700	131 300	0.11
Hypertension	25%	26%	0.72
Diabetes	5%	5%	0.92
Injection drug use as HIV transmission factor	37%	39%	0.71
Regimen cornerstone			
NNRTI	51%	44%	0.10
PI/r	48%	50%	0.74
Protease inhibitor (unboosted)	1%	6%	0.05

CI, confidence interval; eGFR, estimated glomerular filtration rate; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.

[a]Patient data were censored after 720 days.

Table 2

Multivariate associations with 25% estimated glomerular filtration rate decline.

	Hazard ratio	95% CI
TDF vs. NRTI use	1.04	0.68–1.59
Age >45 years	2.31	1.44–3.69
Race (black)	1.52	0.85–2.72
CD4 cell count <200 cells/μl (baseline)	2.66	1.65–4.29
Hypertension	1.56	1.00–2.45
PI/r	2.14	1.37–3.34

CI, confidence interval; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.