

Changes in Renal Function Associated with Tenofovir Disoproxil Fumarate Treatment, Compared with Nucleoside Reverse-Transcriptase Inhibitor Treatment

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In our large observational cohort, use of tenofovir disoproxil fumarate ($n = 344$) was associated with a greater decline in renal function than was use of alternative nucleoside analogues ($n = 314$). Other associations included a lower CD4 cell count, decreased renal function at baseline, and diabetes. The declines were modest and did not lead to greater rates of discontinuation of therapy.

Tenofovir disoproxil fumarate (TDF) is the first nucleoside reverse-transcriptase inhibitor (NRTI) approved by the US Food and Drug Administration for the treatment of HIV disease. It is renally excreted via a combination of glomerular filtration and active tubular secretion. Adefovir dipivoxil, a related NRTI, caused proximal renal tubular dysfunction at a dosage of 60–120 mg/day, which is required to inhibit HIV replication [1]. However, in clinical trials, TDF has demonstrated an excellent renal safety profile. In the Gilead Sciences 903 trial, in which 299 treatment-naïve patients received TDF in combination with lamivudine and efavirenz, there were no instances of renal failure or grade 3/4 elevations in the serum creatinine level through 144 weeks, and there were no significant differences in renal function, compared with that of patients taking stavudine [2, 3].

Nevertheless, renal impairment, including but not limited to proximal renal tubular dysfunction, has been reported to be associated with TDF use [4–11]. The majority of cases of renal impairment have occurred in patients with underlying systemic

or renal disease or in patients taking nephrotoxic agents. However, some cases have occurred in patients without any identified risk factor. Coadministration of TDF with drugs eliminated by active tubular secretion may increase concentrations of either tenofovir or the coadministered drug because of competition for this pathway, and drugs that decrease renal function may increase the concentration of tenofovir.

The reports of renal dysfunction in TDF-treated patients raise concerns about the potential for nephrotoxicity with use of this drug. We analyzed data from a large clinical database to assess the effect of treatment with TDF on renal function in clinical practice.

Methods. We analyzed data from the Johns Hopkins HIV Clinical Cohort. The methods of data collection for this observational longitudinal cohort have been described [12]. This analysis focuses on all patients who started therapy between 1 January 2001 and 31 December 2003 with either TDF or an alternative NRTI as part of a HAART regimen. All data regarding prescribed antiretroviral use was collected by dates of use and dose. Creatinine clearance (CL_{Cr}) was calculated using the Cockcroft-Gault equation, which estimates CL_{Cr} on the basis of the serum creatinine level, weight, and sex of the patient [13]. CL_{Cr} was calculated using the average of the 2 serum creatinine levels determined closest to initiation of therapy. For each subject, the maximum serum creatinine level of those measured within 1 year after initiation of and during the treatment regimen was determined. The subsequent (or preceding, if missing) measurement of serum creatinine was averaged with the maximum level to obtain the value used to calculate the change in CL_{Cr} . The average of the 2 measurements was used to calculate CL_{Cr} to minimize regression to the mean.

We calculated the absolute and percentage change in CL_{Cr} from baseline for each patient and compared these changes in TDF-treated patients with those in NRTI-treated patients. We also assessed the associations of other variables with change in CL_{Cr} , including age, ethnicity, sex, HIV transmission risk factor, diabetes status, hypertension status, CL_{Cr} at baseline, CD4 cell count and HIV-1 RNA load, and concurrently administered antiretroviral agents. The Wilcoxon rank sum test was used for bivariate comparisons with the percent change in CL_{Cr} . Multivariate least-squares linear regression was used to assess the associations of multiple factors with percent change in CL_{Cr} . We plotted the mean values (and standard error) of CL_{Cr} at baseline and at 3-month intervals after initiation of treatment for 1 year. We used Student's t test to compare the change

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between the mean value at baseline with the mean value at each time interval for the 2 groups.

Results. A total of 344 patients received TDF, and 314 patients received an alternative NRTI. The characteristics of the sample are shown in table 1. There were no substantive differences between the groups, except for the expected greater use of alternative NRTIs in the NRTI group, the greater use of lopinavir-ritonavir in the TDF group, and the greater use of efavirenz among patients receiving NRTIs. It is now recommended that the dosing interval of TDF be modified for patients with a CL_{Cr} of <50 mL/min [14, 15]. Only 2 patients, who had a serum creatinine level of >2.0 mg/dL at baseline, received <300 mg of TDF per day.

Table 2 shows serum creatinine levels and CL_{Cr} at baseline

and changes in serum creatinine levels and CL_{Cr} over the period of treatment. The TDF group had significantly greater increases in serum creatinine levels and decreases in absolute and percentage CL_{Cr} , compared with the NRTI group. There was no difference in the rate of discontinuation of treatment coincident with maximum decline in CL_{Cr} : only 19 (5.5%) of TDF-treated patients and 21 (6.7%) of NRTI-treated patients discontinued therapy at the time of maximum decline in renal function.

Figure 1 shows the change in CL_{Cr} from the start of treatment through day 365 of therapy (in 90-day increments). It can be seen that the change in CL_{Cr} was apparent after 90 days of therapy and persisted for the entire year.

In addition, regarding the comparison of TDF use with use of other NRTIs, diabetes was associated with a -13% change

Table 1. Demographic and clinical characteristics of patients who received tenofovir disoproxil fumarate and patients who received nucleoside reverse-transcriptase inhibitors.

Characteristic	TDF group (n = 344)	NRTI group (n = 314)
Sex, no. (%) male	249 (72.4)	222 (70.7)
Ethnicity, no. (%)		
White	100 (29.1)	73 (23.2)
African American	244 (70.9)	241 (76.8)
HIV transmission risk factor, no. (%)		
MSM	129 (37.5)	96 (30.6)
Injection drug use	121 (35.2)	112 (35.7)
Other	94 (27.3)	106 (33.8)
Age, median years (1st, 3rd quartiles)	38 (34, 43)	38 (32, 45)
Diabetes mellitus, no. (%)	42 (12.2)	26 (8.3)
Hypertension, no. (%)	85 (24.7)	63 (20.1)
CD4 cell count, median cells/mm ³ (1st, 3rd quartiles)	220 (77, 433)	214 (94, 380)
HIV-1 RNA load, median copies/mL (1st, 3rd quartiles)	15,300 (146, 124,900)	9700 (168, 149,400)
Concomitant ART received, no. (%)		
Lopinavir/ritonavir	103 (29.9)	44 (14.0) ^a
Nelfinavir	2 (<1)	11 (3.5)
Indinavir/ritonavir	2 (<1)	15 (4.8)
Saquinavir/ritonavir	1 (<1)	1 (<1)
Amprenavir/ritonavir	16 (4.7)	5 (1.6)
Efavirenz	32 (9.3)	69 (22.0) ^a
Nevirapine	8 (2.3)	6 (1.9)
Abacavir	87 (25.3)	223 (71.0) ^a
Zidovudine	80 (23.3)	229 (72.9) ^a
Didanosine	9 (2.6)	27 (8.6) ^a
Stavudine	2 (<1)	25 (8.0) ^a
Lamivudine	124 (36.1)	248 (79.0) ^a
HAART received, no. (%)		
Initial	47 (13.4)	121 (38.5) ^a
Subsequent	297 (86.6)	193 (61.5) ^a

Note. ART, antiretroviral therapy; MSM, men who have sex with men.

^a $P < .05$ for comparison of TDF and NRTI groups.

Table 2. Comparison of change in renal function between patients who received tenofovir disoproxil fumarate (TDF) and patients who received nucleoside reverse-transcriptase inhibitors.

Variable	TDF group (n = 344)	NRTI group (n = 314)	P
Serum creatinine level at start of treatment, mg/dL	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	.56
CL _{Cr} at start of treatment, mL/min	117 (95, 148)	118 (92, 177)	.69
Treatment period, days	303 (169, 365)	336 (175, 365)	.19
Maximum serum creatinine level, mg/dL	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	.17
Absolute change in serum creatinine level, mg/dL	+0.15 (+0.05, +0.30)	+0.10 (0.0, +0.25)	.01
Calculated minimum CL _{Cr} , mL/min	98 (71, 125)	102 (79, 129)	.43
Absolute change in CL _{Cr} , mL/min	-13.3 (-24.0, 0.0)	-7.5 (-20.5, +6.5)	.005
Percent change in CL _{Cr} , %	-10 (-22, 0)	-6 (-17, +6)	.007
Patients with decline in CL _{Cr} , no. (%)			
>50% decline	15 (4.4)	6 (1.9)	.14 ^a
25%–50% decline	46 (13.4)	34 (10.8)	
1%–25% decline	158 (45.9)	141 (44.9)	
≤0% decline ^b	125 (36.3)	133 (42.3)	

NOTE. Data are median value (1st, 3rd quartiles), unless otherwise indicated. CL_{Cr}, creatinine clearance.

^a P for trend.

^b CL_{Cr} same or improved.

in CL_{Cr} (vs. a change of -8% in patients without diabetes [$P < .04$]); a baseline CD4 cell count of <50 cells/mm³ was associated with a change of -14% (vs. a change of -8% for patients with a baseline count of >50 cells/mm³ [$P < .01$]); a baseline HIV-1 RNA load of $>20,000$ copies/mL was associated with a change of -15% (vs. a change of -8% for patients with a baseline load of $>20,000$ copies/mL [$P < .02$]); and receipt of initial HAART was associated with a change of -11% (vs. a change of -8% for patients who received HAART subsequently [$P < .03$]). Hypertension status, age, sex, ethnicity, the presence of concomitant hepatitis C or B, use of lopinavir/ritonavir, or use of any other specific protease inhibitor or NRTI were not associated with the percent change in CL_{Cr} ($P > .05$).

Adjusting for these variables in a multivariate analysis, only TDF use ($P = .006$) and a CD4 cell count of <50 cells/mm³ ($P < .001$) were associated with CL_{Cr} decline. A baseline CL_{Cr} value of <50 mL/min and diabetes were less strongly associated ($P = .10$). Because the dosage of TDF was only adjusted for poorer renal function (defined as a CL_{Cr} of <50 mL/min) in 2 patients, the multivariate analysis was repeated for those patients with a baseline CL_{Cr} of >50 mL/min. The results were similar; TDF use ($P = .004$), a low CD4 cell count ($P < .001$), and diabetes ($P = .06$) were associated with CL_{Cr} decline. In both analyses, hypertension status, use of lopinavir-ritonavir or other antiretroviral agents, HIV-1 RNA load, previous use of adefovir dipivoxil, age, sex, ethnicity, and HIV transmission risk factor were not associated with CL_{Cr} decline, after adjustment for the variables in table 2.

Discussion. TDF use has not been associated with nephrotoxicity in clinical trials [2, 3, 16–18]. However, it has been suggested that clinical trials may not represent “real world”

scenarios, because patients with renal insufficiency or risk factors for renal insufficiency are often excluded. Data from clinical cohorts are somewhat conflicting. Although several studies have shown little evidence that nephrotoxicity is associated with use of TDF [19–23], other studies have shown evidence of an association with a modest decline in renal function [24–29].

In our study, TDF use was associated with a significantly greater decline in CL_{Cr}, compared with the decline associated

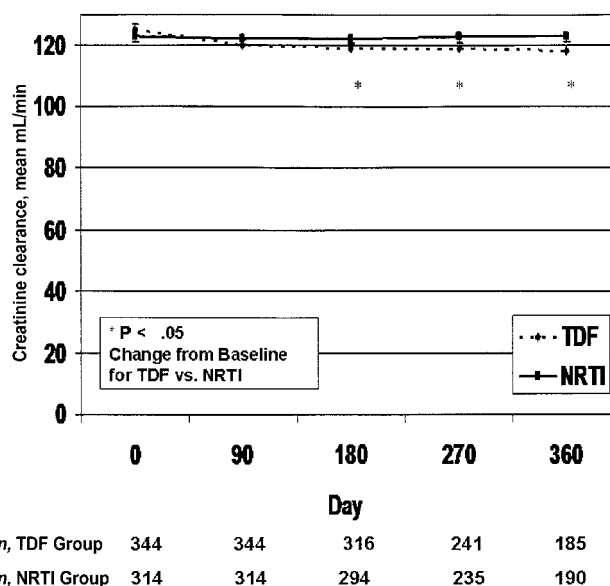


Figure 1. Plot of mean (with standard error) CL_{Cr} over time for patients who received TDF and patients who received other NRTIs (last CL_{Cr} on treatment carried forward if treatment stopped).

with the use of alternative NRTIs. The relative decline in CL_{Cr} associated with the use of TDF, compared with that associated with the use of alternative NRTIs, was 4%. To minimize temporal bias, the period of treatment with NRTI was kept within the same study period as treatment with TDF. Because this was an observational study, and because urinalysis and serum phosphate analysis are not performed routinely in our clinic, we could not assess the frequency of proteinuria or Fanconi syndrome.

In addition to TDF use, the other variable strongly associated with CL_{Cr} decline was advanced immunosuppression (defined as a CD4 cell count of <50 cells/mm³). There were trends toward associations with diabetes and with a baseline CL_{Cr} of <50 mL/min. With the exception of only 2 patients, the dosage of TDF was 300 mg/day for all patients. Whether a lower dose of TDF for patients with a lower CL_{Cr} at initiation of therapy would have modified the decrease in CL_{Cr} is unknown. However, when restricting our analysis to patients with a baseline CL_{Cr} of >50 mL/min—patients who should receive full doses of TDF, according to current dosing recommendations [15]—we found the same modest decline in renal function. Patients who received treatment with TDF were less likely to be receiving initial HAART than were patients who received treatment with other NRTIs. However, receipt of initial HAART was not associated with CL_{Cr} decline, compared with receipt of subsequent HAART.

It is possible that the emerging difference between CL_{Cr} decline associated with TDF use and that associated with the use of other NRTIs is a result of a longer duration of treatment. In an earlier analysis of these data [30], which found no significant difference in renal function, the median treatment duration was 246 days, compared to 322 days for the current analysis. More patients who received TDF were also taking lopinavir-ritonavir, which has been shown to increase tenofovir levels [31]. However, concomitant use of lopinavir-ritonavir or other antiretroviral drugs was not associated with CL_{Cr} decline.

Although statistically significant, the decline in CL_{Cr} associated with TDF use was small and was not associated with a greater rate of discontinuation, probably because the changes in creatinine levels appeared trivial to the clinician. Because the majority of these patients continue to receive treatment, we will continue to observe this cohort to assess renal function changes as the duration of treatment increases.

There may be a modest decline in renal function in TDF-treated patients with prolonged use, especially in patients with advanced HIV disease, diabetes, or a decreased renal function at baseline. The clinical significance of these findings is unclear. Because the decrease in CL_{Cr} was gradual and did not lead to clinically significant renal failure, there is no reason to withhold treatment with TDF from patients who would benefit from it. However, the data from our large cohort emphasize the im-

portance of assessing renal function prior to initiation of such treatment, making appropriate dose adjustments for patients with impaired renal function at baseline, and monitoring changes in renal function in TDF-treated patients.

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References

1. Benhamou Y, Bouchet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* **2001**;358:718–23.
2. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. *JAMA* **2004**;292:191–201.
3. Staszewski S, Gallant JE, Pozniak AL, et al. Three-year analysis of the renal safety of tenofovir DF (TDF) vs. stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients [abstract WePeB5917]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
4. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. *Am J Kidney Dis* **2002**;40:1331–3.
5. Créput C, Gonzales-Canali G, Hill G, Piketti C, Kazatchkine M, Nochy D. Renal lesions in HIV-1-positive patient treated with tenofovir. *AIDS* **2003**;17:935–7.
6. Schaaf B, Aries SP, Kramme E, et al. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis* **2003**;37:e41–3.
7. Blick G, Greiger-Zanlungo P, Garton T, Hatton E, Lopez RJ. Tenofovir may cause severe hypophosphatemia in HIV/AIDS patients with prior adefovir-induced renal tubular acidosis [abstract 717]. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections (Boston). **2003**.
8. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* **2003**;36:1070–3.
9. Peyrière H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J Acquir Immune Defic Syndr* **2004**;35:269–73.
10. Coca S, Perazella MA. Acute renal failure associated with tenofovir: evidence of drug-induced nephrotoxicity. *Am J Med Sci* **2002**;324:342–4.
11. Gaspar G, Monereo A, Garcia-Reyne A, de Guzman M. Fanconi syndrome and acute renal failure in a patient treated with tenofovir: a call to action. *AIDS* **2004**;18:351–2.
12. Moore RD. Understanding the clinical and economic outcomes of HIV therapy: the Johns Hopkins HIV clinical practice cohort. *J Acquir Immune Defic Syndr Hum Retrovirol* **1998**;17(Suppl 1):S38–41.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* **1976**;16:31–41.
14. Kearney BP, Liaw S, Yale K, et al. Pharmacokinetics following single dose administration of tenofovir DF in subjects with renal impairment [poster P4]. In: Program and abstracts of the 6th International Congress on Drug Therapy in HIV (Glasgow). **2002**.
15. Viread [package insert]. Foster City, California: Gilead Sciences, **2004**.
16. Squires K, Pozniak AL, Pierone G, et al. Tenofovir DF in antiretroviral-

- experienced, nucleoside-resistant HIV-1 infected patients with incomplete viral suppression. *Ann Intern Med* **2003**;139:313–20.
17. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* **2002**;16:1257–63.
 18. Izzedine H, Isnard-Bagnis C, Hulot J-S, et al. Renal safety of tenofovir in HIV-experienced patients. *AIDS* **2004**;18:1074–6.
 19. Gallais H, Lazzarin A, Adam A, et al. The Viread Expanded Access Program (EAP) in Europe/Australia: summary of the safety and efficacy of tenofovir disoproxil fumarate (TDF) in antiretroviral treatment (ART) experience patients [abstract TuPeB4552]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 20. Jones R, Stebbing J, Nelson N, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case control study. *J Acquir Immune Defic Syndr* **2004**;37:1489–95.
 21. Scott JD, Wolfe PR, Quiros J, Behrooznia E, Buyer B, Bolan RK. Rare occurrence of renal toxicity when retrospectively evaluating the use of tenofovir DF in 2 clinical practices [abstract uPeB4532]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 22. Lewis S, Gathe J, Ebrahimi R, Flaherty J, Wallace RJ. Comparative evaluation of renal function (RF) in HIV-infected, treatment-naïve patients of African American (AA) descent receiving HAART regimens containing either tenofovir DF (TDF) or zidovudine [abstract TuPeB4599]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 23. Roca B, Gisbert C, Cabestany B, Perez AP, Ventura JM. Metabolic and renal profile before and after tenofovir DF [abstract B10708]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 24. Jaegel-Guedes E, Wolf E, Ruemmelein N, et al. Incidence of tenofovir-related nephrotoxicity in a large outpatient cohort [abstract WePeB5937]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 25. Horberg MA, Klein DB, Yu J, Sinn K, Yu J. Effect of tenofovir on renal function in a “real world” clinic setting [abstract WePpB2066]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 26. Mauss S, Berger F, Carls H, Schmutz G. Tenofovir is associated with mild renal dysfunction [abstract WePeB5941]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 27. Chin-Beckford N, Kaul S, Jayaweera DT. Comorbidities drive nephrotoxicity associated with tenofovir fumarate. A case series from Florida [abstract WePeB5970]. In: Program and abstracts of the XV International AIDS Conference (Bangkok). **2004**.
 28. Harris M, Zalunardo N, Bonner S, Werb R, Valyi M, Montaner JSG. Use of estimated glomerular filtration rate to predict renal toxicity in patients receiving tenofovir DF [abstract 750]. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (San Francisco). **2004**.
 29. Harris M, Zalunardo N, Yip B, et al. Nephrotoxicity of tenofovir DF [abstract 168rsqb]. In: Program and abstracts of the 12th Annual Canadian Conference on HIV/AIDS Research (Halifax). **2003**.
 30. Parish MA, Gallant JE, Moore RD. Changes in renal function in patients treated with tenofovir DF (TDF) vs. nucleoside reverse transcriptase inhibitors (NRTIs) [abstract 751]. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (San Francisco). **2004**.
 31. Kearney B, Mittan A, Sayre J, et al. Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir [abstract A-1617]. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). **2003**.