

Renal Dysfunction With Tenofovir Disoproxil Fumarate—Containing Highly Active Antiretroviral Therapy Regimens Is Not Observed More Frequently

A Cohort and Case-Control Study

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Background: Tenofovir disoproxil fumarate (tenofovir DF), the first nucleotide analogue reverse transcriptase inhibitor approved for the treatment of HIV infection, has been associated with renal dysfunction in isolated cases. We investigated the overall incidence and risk of renal dysfunction in individuals receiving tenofovir DF and compared this with other antiretrovirals.

Methods: Data from the Chelsea and Westminster cohort were analyzed to reveal HIV-positive individuals with a creatinine value greater than 120 $\mu\text{mol/L}$ at any time, the upper limit of normal used by our reference laboratory. These individuals were classified according to antiretroviral exposure and time exposed. A matched case-control study was performed comparing patients who had received tenofovir DF and subsequently developed a creatinine value greater than 120 $\mu\text{mol/L}$ against controls who had been treated with tenofovir DF and had not experienced a creatinine elevation.

Results: Of 4183 HIV-positive patients, 1175 were identified as having a recorded creatinine value $>120 \mu\text{mol/L}$. Comparison of antiretroviral-naïve patients and patients exposed to tenofovir DF- and non-tenofovir DF-containing regimens revealed a lower rate ratio and probability of developing a creatinine value $>120 \mu\text{mol/L}$ in patients exposed to tenofovir DF (rate ratio vs. no antiretrovirals = 0.22, 95% confidence interval [CI]: 0.07–0.69; $P < 0.001$) with no significant difference between HAART regimens, corrected for duration of exposure. Of the 1058 individuals who were exposed to tenofovir DF, 84 (8%) patients experienced a creatinine value $>120 \mu\text{mol/L}$ subsequent to exposure. An alternative etiology of renal dysfunction was found in 75 (90%) of these individuals.

Conclusions: Tenofovir DF is not associated with renal dysfunction more frequently than other antiretroviral drugs, and the occurrence of renal dysfunction in this context is usually attributable to other causes.

Key Words: tenofovir DF, highly active antiretroviral therapy, renal, cohort, creatinine

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The selective targeting of the HIV-1 protease and/or reverse transcriptase has led to decreased morbidity and mortality as a result of infection with HIV-1.^{1,2} Tenofovir disoproxil fumarate [*R*-9-(2-phosphonyl-methoxypropyl)adenine, tenofovir DF] is the first nucleotide analogue reverse transcriptase inhibitor (NRTI) to be approved for the treatment of HIV infection.^{3–6} It has been well tolerated in clinical trials to date, without evidence of long-term toxicity in cohort studies, including the mitochondrial toxicity that has been associated with some NRTIs.^{7,8} Since its approval in October 2001, tenofovir DF has quickly become a widely used component of antiretroviral regimens for treatment-naïve and -experienced patients.^{9–11} Recent data also indicate that it is able to overcome lamivudine resistance in the treatment of hepatitis B virus.^{12–14}

Cidofovir and adefovir dipivoxil, compounds structurally related to tenofovir DF, have been associated with increased risk for acute renal insufficiency possibly because of tubular accumulation and toxic metabolites.^{15–17} A small number of cases of tubular injury associated with Fanconi-like syndrome (proximal renal tubular acidosis) in patients with normal baseline renal function have also been reported.^{18,19} Although there are other isolated cases of renal tubular dysfunction and a report of acute renal failure in a patient with stable chronic renal failure during tenofovir DF therapy,^{20,21} the frequency of these occurrences in HIV-1-infected individuals receiving tenofovir DF relative to other antiretroviral regimens remains unknown.

Although renal insufficiency is well reported in the context of HIV-1 infection and its treatment,^{16,22} because of the

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specific case reports of acute renal failure during tenofovir DF therapy, we investigated the prevalence of renal insufficiency in a large cohort of HIV-1–positive individuals. In comparing such individuals with appropriately matched controls, we established that tenofovir DF does not cause renal failure more frequently than other antiretrovirals and that the occurrence of renal failure in this context is a rare event.

METHODS

The Chelsea and Westminster HIV cohort is one of the largest in Europe, and we prospectively collect routine data on the individuals who attend. HIV-positive patients are seen at regular intervals for clinical assessment; trial follow-up; and biochemical, immunologic, and virologic assessments. We have defined highly active antiretroviral therapy (HAART) as therapy consisting of at least 3 antiretroviral drugs in accordance with published guidelines.²³ HAART was begun at this institution on January 1, 1996.

Our reference laboratory denotes 120 $\mu\text{mol/L}$ as the value representing the upper limit of normal for creatinine in men and women. Thus, we defined renal dysfunction as a creatinine value greater than 120 $\mu\text{mol/L}$ at any time and then classified patients according to antiretroviral exposure before this level. Patients who received nucleoside analogue only regimens and those with no antiretroviral history were also examined. The data were analyzed using the Genmod procedure in SAS version 8.0 with \log_e link and Poisson error distributions. If creatinine levels were greater than 120 $\mu\text{mol/L}$, NRTI exposure before a creatinine level $>120 \mu\text{mol/L}$ was used; otherwise, the antiretroviral agents at the time of censoring were recorded. Time-dependent variables were studied to investigate the probability of developing a creatinine level $>120 \mu\text{mol/L}$ on different antiretroviral regimens that did and did not contain tenofovir DF.

For the matched case-control study, any patient who had received tenofovir DF and had a creatinine value greater than 120 $\mu\text{mol/L}$ since commencing tenofovir DF (and not before) was identified. Each of these patients was matched to a control who had received tenofovir DF but did not have a raised creatinine value since beginning this antiretroviral. The matching criteria used included (1) line of treatment (experienced with other NRTIs vs. not experienced), (2) inpatient episode while on tenofovir DF for any reason, (3) total duration of combination therapy at the time of starting tenofovir DF (± 2 months), (4) baseline CD4 count (± 50 cells/ mm^3), and (5) baseline HIV-1 viral load ($\pm 10,000$ copies/mL). Data were analyzed in SAS using conditional logistic regression with the Proportion Hazard Regression Model (PHREG) procedure by using the discrete logistic model stratified by the aforementioned criteria.

In those patients receiving tenofovir DF who developed a creatinine level greater than 120 $\mu\text{mol/L}$, we compared changes in their creatinine from pre-tenofovir DF levels to peak levels and latest creatinine values. Creatinine clearance

was calculated in these patients using the formula (the Cockcroft and Gault equation):

$$\text{Creatinine Clearance (mL/min)} = \frac{F \times (140 - \text{Age}) \times \text{IBW (kg)}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

where $F = 1.04$ (female patients) and $F = 1.23$ (male patients) and ideal body weight (IBW in kilograms) = $Y + (0.906 \text{ to each centimeter greater than } 152.4 \text{ cm})$, where $Y = 45.5$ (female patients) and $Y = 50$ (male patients). We also calculated creatinine clearances according to the Jelliffe and Chatelut equations.

We performed clinical record searches on all these individuals to establish the presence or absence of any other cause or contributors to renal failure, including nephrotoxic drugs and/or serious intercurrent infections and/or physiologic insult culminating in a decline in renal function. Weights were recorded to establish creatinine clearance. The cause of death for any patient receiving tenofovir DF was also investigated.

In a small audit to investigate the presence of proteinuria in our patients, 100 individuals' urine samples were dipsticked (Dipsticks; Bayer, Newbury, UK) before and during tenofovir DF treatment. The presence or absence of albuminuria as detected by the dipsticks was recorded at time 0 and 8 to 12 weeks after beginning therapy.

RESULTS

Comparison With Other Antiretrovirals

At this institution, 4183 HIV-1–positive individuals have been followed up during the HAART era, and of these, we have identified 1175 (28%) patients who have ever had a creatinine value greater than 120 $\mu\text{mol/L}$. In comparison with having received no antiretroviral regimen and receiving regimens containing and not containing tenofovir DF, we observed a lower rate ratio of developing a creatinine level greater than 120 $\mu\text{mol/L}$ in those patients who received tenofovir DF corrected for length of time exposed (Fig. 1). The differences in rate ratios between all HAART regimens that patients were exposed to were not statistically significant after adjustment for duration of exposure (Table 1).

No use of antiretrovirals was a significant risk factor for an increased creatinine level (see Fig. 1). We observed a statistically significant increase in the incidence of HIV-positive individuals having a creatinine value greater than 120 $\mu\text{mol/L}$ in those individuals who had no history of antiretrovirals (rate ratio = 3.32, 95% confidence interval [CI]: 2.75–3.97; $P < 0.001$). In addition, nucleoside analogue exposure only (rate ratio = 1.87) was more likely to be associated with an increased creatinine level compared with nucleoside analogue and non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy (rate ratio = 1.13) or nucleoside analogue and protease inhibitor (PI) and NNRTI therapy. Those individuals who received a nucleoside analogue– and PI-containing HAART regimen

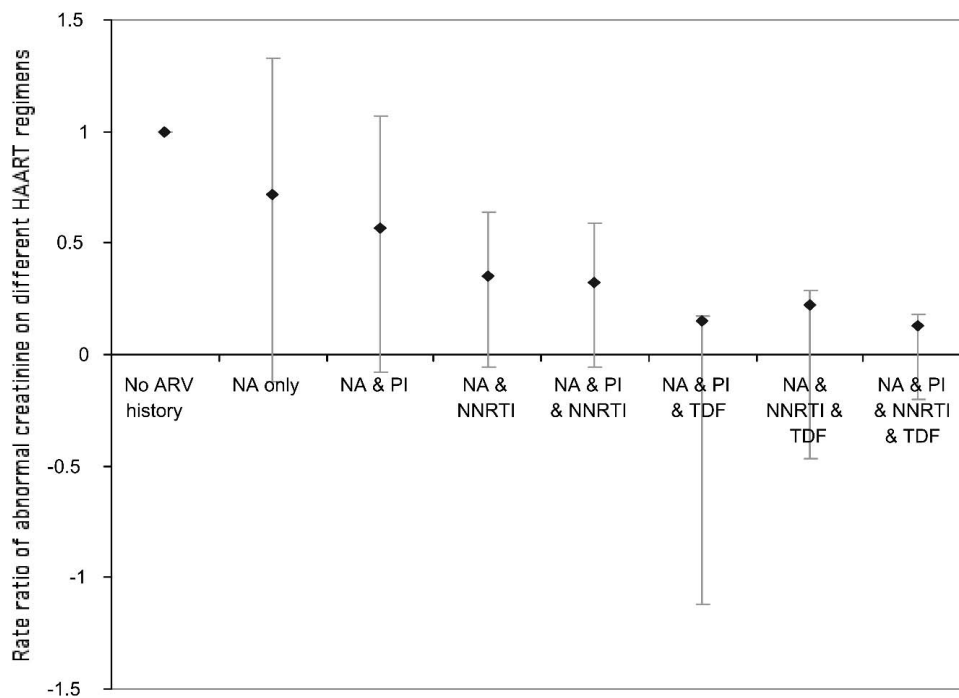


FIGURE 1. Rate ratio of abnormal creatinine levels for different antiretroviral regimens. No antiretroviral history was used as the reference category. ARV indicates, antiretroviral; NA, nucleoside analogue; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

(rate ratio = 1.87) were not significantly less likely to have a creatinine value greater than 120 µmol/L than those who received a nucleoside analogue only because of wide CIs in the former group (95% CI: 1.53–2.31).

Consistent with these data, the probability of developing a raised creatinine level over time was not significantly increased in those individuals who received tenofovir DF-containing regimens (Fig. 2). Figure 2 also demonstrates that the probability of developing a raised creatinine level over time is similar for those patients who did not receive antiretrovirals or received nucleoside analogues only.

Matched Cohort Study

Using data extracted on September 30, 2003, we identified 1058 patients who have never been prescribed tenofovir DF. Of these, 117 patients were observed to have a creatinine level greater than 120 µmol/L (once), and 33 (28%) of these 117 patients were excluded from matching because of a creatinine level greater than 120 µmol/L before receiving tenofovir DF. Table 2 demonstrates that for the 84 patients who were successfully matched 1:1 with controls, there were no statistically significant differences in renal parameters (ie, creatinine or phosphate) measurements.

TABLE 1. Total Number of Days at Risk on Different Antiretroviral Regimens

		Total Patient-Years at Risk 32,575
Antiretroviral class exposure (if creatinine >120, then exposure before creatinine >120; otherwise, at the time of censoring)	No antiretroviral history	7589
	NA only	2409
	NA + PI only	4524
	NA + NNRTI only	5592
	NA + PI + NNRTI	5925
	NA + PI + TFV	899
	NA + NNRTI + TFV	1493
	NA + PI + NNRTI + TFV	4144

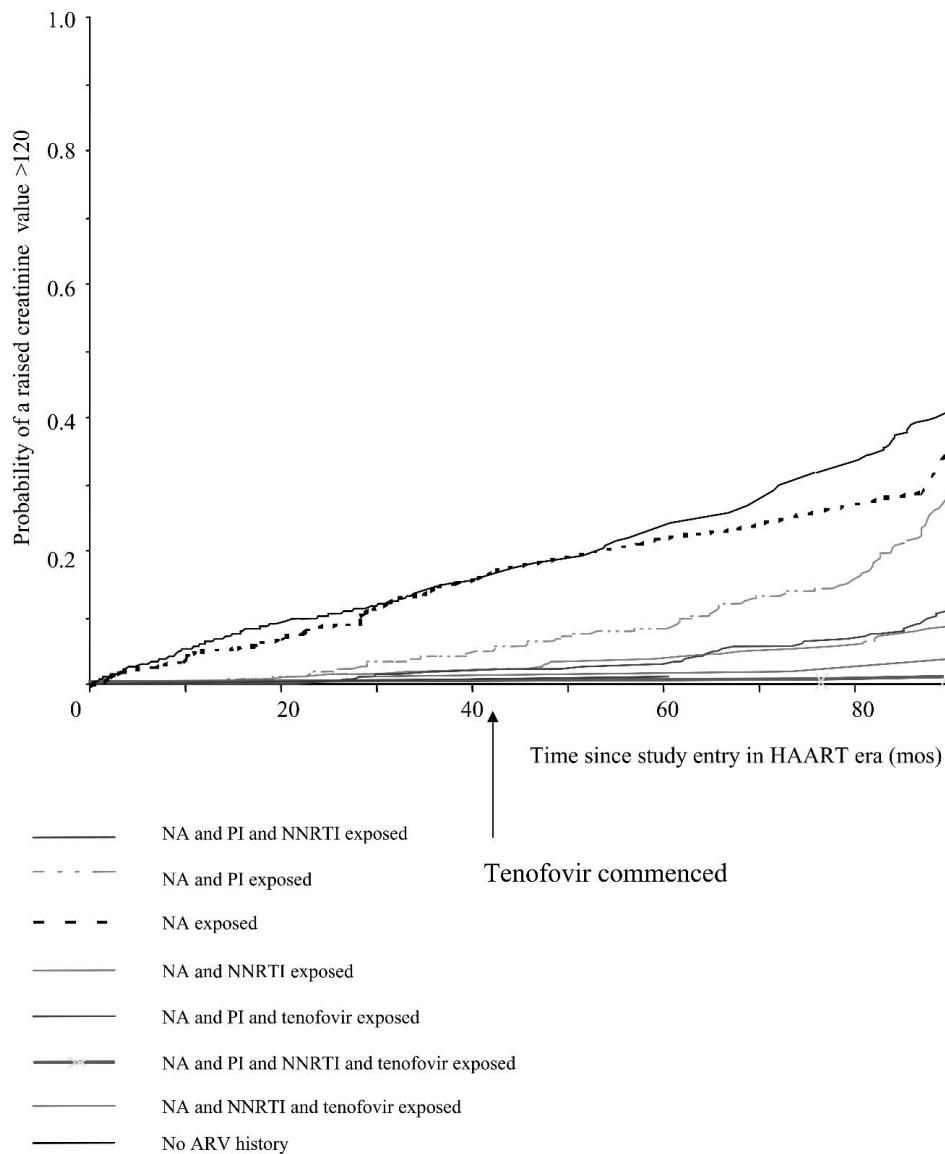


FIGURE 2. Probability of developing an increased creatinine value over time for different antiretroviral regimens. Tenofvir disoproxil fumarate was begun at this institution on January 1, 2000. ARV indicates antiretroviral; NA, nucleoside analogue; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Follow-Up of Patients

Of the 84 patients who developed a raised creatinine level subsequent to receiving tenofvir DF, analysis of patient records revealed the presence of other causes of renal impairment in 75 patients (Table 3). This included nephrotoxic drugs in 13 (15%), serious intercurrent illnesses in 21 (25%), and both in 10 (12%). The baseline characteristics of these individuals, including demographic, ethnic, immunologic, and virologic data, were not significantly different from those of the remainder of the cohort. In 9 individuals exposed to tenofvir DF, creatinine values increased to greater than 120 $\mu\text{mol/L}$ without definite obvious other causes. Three of these individu-

als had recently received short courses (5 days) of high-dose co-trimoxazole for presumptive *Pneumocystis carinii* pneumonia (PCP).

The median creatinine and creatinine clearances before tenofvir DF, at the peak during tenofvir DF, and at the latest values are shown in Figure 3. The rise in creatinine observed in these individuals had partially normalized by the time of the most recent sample. Similarly, the 33 patients who began tenofvir DF with a creatinine value greater than 120 $\mu\text{mol/L}$ showed no significant increases or decreases. There were no correlations observed between CD4 cell count and creatinine or phosphate values at start, peak, or the latest creatinine or

TABLE 2. Patients Receiving Tenofovir DF Who Developed a Creatinine Value Greater Than 120 µmol/L Were Matched 1:1 With Patients Receiving Tenofovir DF and a Creatinine That Remained in the Normal Range

Matching Variables		All Started Tenofovir DF	
		Controls Creatinine <120 µmol/L (n = 84)	Cases Creatinine ≥120 µmol/L (n = 84)
Line of treatment	First	11 (13.1)	11 (13.1)
	≥2	73 (86.9)	73 (86.9)
Inpatient episode	No	45 (53.6)	45 (53.6)
While on tenofovir DF	Yes	39 (46.4)	39 (46.4)
Baseline CD4 cells/mm ³		191 (105–353)	158 (81–358)
Baseline HIV viral load copies/mL		2345 (<500–69,170)	2605 (<500–105,522)
Total duration on combination before starting tenofovir DF (wk)		49 (13–69)	49 (8–80)
Baseline phosphate (mmol/L)		(n = 70) 1.0 (0.8–1.1)	(n = 71) 1.1 (0.9–1.2)
Phosphate at abnormal creatinine or at end of first tenofovir DF therapy		(n = 75) 1.1 (0.9–1.2) Range: 0.5–1.9	(n = 79) 1.0 (0.9–1.2) Range: 0.4–1.96

TABLE 3. Other Factors Affecting Renal Function in 84 Individuals Who Developed a Creatinine Value Greater Than 120 µmol/L After Starting Tenofovir DF

Clinical Event	No. Patients
Concurrent medical diagnosis*	21
Nephrotoxic drug exposure†	13
Medical diagnosis and nephrotoxic drug exposure	10
Transient rise in creatinine only‡	15
Transient creatinine rise and medical diagnosis	4
Previous indinavir exposure	3
Indinavir exposure and medical diagnosis	2
Indinavir exposure and medical diagnosis and nephrotoxic drug exposure	1
Indinavir exposure and transient creatinine rise	1
Other	9
Total	84

The median age of these individuals was 43 years; approximately half (47%) were receiving tenofovir DF as part of a first HAART regimen, and the remainder were receiving tenofovir DF as part of a second regimen.

*Concurrent medical diagnoses included at least 1 of the following relevant causes of acute/chronic renal failure: sepsis, acute dehydration, proven urinary tract infection, and liver failure leading to hepatorenal syndrome.

†Nephrotoxic drugs included concurrent administration for longer than 5 days of at least 1 of the following: nonsteroidal anti-inflammatory drugs, aminoglycosides, foscarnet, angiotensin-converting enzyme inhibitors, ganciclovir, and amphotericin.

‡Transient creatinine rise is defined as a single elevated creatinine value recorded during exposure to tenofovir DF therapy and returning to baseline within a 1-month period.

phosphate value (Pearson correlation coefficient, $r < 0.02$ in all cases). A retrospective analysis of phosphate values 3 months before the peak creatinine value demonstrated insignificant positive or negative predictive values.

African-American patients comprised less than 10% of our cohort, and subgroup analyses here showed no notable differences. Furthermore, in an individual audit of 100 patients examined for the presence or absence of proteinuria before and during tenofovir DF therapy, we observed no changes in the presence of albuminuria as detected by dipstick. Fifteen patients died while receiving tenofovir DF; most of these individuals (64%) died secondary to sepsis. Importantly, tenofovir DF-induced renal failure was not a cause of death in any patient.

DISCUSSION

This cohort and case-controlled study demonstrates that renal failure associated with tenofovir DF is not more common than with other antiretroviral regimens. In 1058 individuals exposed to tenofovir DF, a maximum of 9 (<1%) patients developed an increased creatinine level without obvious other causes.

Although trials have reported no significant renal abnormalities in patients receiving tenofovir DF, including those coinfecting with hepatitis B virus, isolated case reports have raised serious concerns regarding “renal safety”.^{18–21} These case reports have included patients recruited in the randomized 907 study, which investigated tenofovir DF in nucleoside-resistant HIV-1 infection.¹⁰ The investigators found that

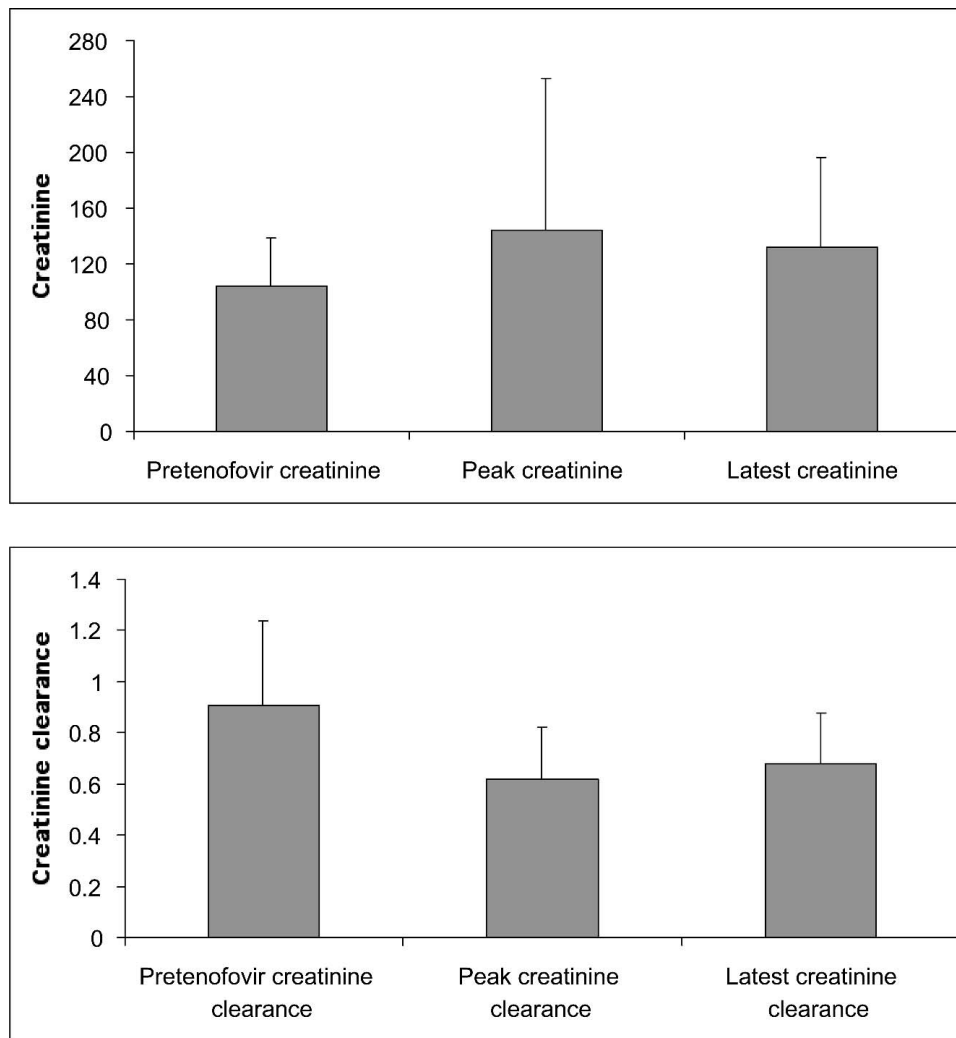


FIGURE 3. Changes in creatinine ($\mu\text{mol/L}$) and creatinine clearance (mL/min) before tenofovir disoproxil fumarate (tenofovir DF), at the peak creatinine level, and at the most recent value in 84 patients in whom creatinine increased to greater than $120 \mu\text{mol/L}$ after administration of tenofovir DF. Median \pm standard deviation is shown. The creatinine clearance shown was calculated using the Cockcroft and Gault equation. No difference was found using the Jelliffe or Chatelut formula to calculate creatinine clearance.

through week 24, the incidence of clinical adverse events was similar between patients receiving placebo and tenofovir DF (14% vs. 13%) and that this was maintained to week 48.

Our study illustrates that nonsignificant changes in creatinine after tenofovir DF exposure may occur (84 [8%] of 1058 patients exposed), although increases are usually associated with other causes of renal impairment and subsequent decreases in creatinine are observed. Interestingly, in 33 patients with a creatinine value greater than $120 \mu\text{mol/L}$ who were prescribed tenofovir DF, an increase in creatinine was not observed and tenofovir DF use was not associated with changes in dipstick-detectable proteinuria.

We found that antiretroviral-naive patients have a statistically significant increased creatinine level and an increased

probability of developing an increased creatinine level during follow-up ($P < 0.001$). Although this may be related to other factors, including noncompliance, hepatitis C virus, and intravenous drug use, the finding is not surprising considering that studies have shown the renal epithelium may represent a specific compartment of HIV-1 replication. Here, in situ hybridization of renal biopsy tissue obtained from individuals with HIV-1 nephropathy suggests that the kidney represents a reservoir of HIV infection even in those patients with an undetectable viral load.^{24,25} The mechanism of in vivo replication in tissues such as the kidney remains unknown, and it also remains unclear whether HIV is truly latent here or whether it represents a slowly replicating pool that is relatively impervious to the effects of HAART.

Because most patients had concurrent reasons for renal dysfunction, it is not possible to attribute the change in creatinine clearance to tenofovir DF exposure alone. Although it is conceivable that tenofovir DF exposure increases the risk of a raised creatinine level in conjunction with other causes of renal nephrotoxicity, these data indicate that this is a generally rare occurrence or that the risk is no greater than with other NRTIs. As with other forms of antiretroviral therapy, idiosyncratic reactions to tenofovir DF have been documented. In our own cohort, the incidence of Fanconi syndrome is limited to 1 suspected case. Here, a 37-year-old man was receiving tenofovir DF therapy as well as zidovudine, didanosine, and delavirdine. He presented with a 2-day history of left ankle swelling, and a magnetic resonance imaging (MRI) scan revealed a stress fracture of the left distal tibia. Bone-derived alkaline phosphatase was measured at 301 IU/L, phosphate at 0.3 mmol/L, and calcium at 1.9 mmol/L. Urinalysis revealed the presence of glycosuria and aminoaciduria, and conservative management, including cessation of tenofovir DF, led to normalization of laboratory parameters. Since acceptance of this paper, we have had two further suspected cases of Fanconi Syndrome in our unit. Again, both patients had concurrent causes of renal dysfunction.

Patients with a raised creatinine level subsequent to receiving tenofovir DF should have other causes of nephrotoxicity eliminated. Although tenofovir DF may be associated with some renal pathologic findings, such events do not occur with an increased incidence in comparison to other antiretrovirals. These data also suggest that over time, such events may be less common in comparison to other regimens. Overall, receiving HAART is associated with improved renal function, as measured by creatinine levels, compared with not receiving HAART.

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