Acute Renal Failure Associated with Tenofovir Treatment in a Patient with Acquired Immunodeficiency Syndrome

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We report a case of acute renal failure due to proximal tubular necrosis associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome.

Tenofovir fumarate is a new nucleotide reverse-transcriptase inhibitor licensed for treatment of HIV infection in patients for whom HIV treatment has failed. Cidofovir and adefovir, compounds closely related to tenofovir, have been associated with increased risk for acute renal insufficiency due to tubular toxicity, possibly induced via mitochondrial DNA depletion [1–3]. To our knowledge, only 1 case of tubular injury with Fanconi syndrome associated with tenofovir use in a patient with normal baseline renal function has been reported [4]. A second case of acute renal failure in a patient with stable chronic renal failure was reported elsewhere [5]. In addition, there were recent cases of renal tubular dysfunction associated with tenofovir treatment reported at the 10th Conference on Retroviruses and Opportunistic Infections [6, 7]. We describe an HIV-infected patient who developed acute renal failure while receiving tenofovir treatment that was due to proximal tubular necrosis without Fanconi syndrome.

Case report. A 51-year-old man with HIV infection and a history of cerebral toxoplasmosis, cytomegalovirus (CMV) gastritis, and chronic hepatitis C without liver cirrhosis was inconsistently treated during 1997–2001 with different antiretroviral combination therapies. No sufficient virologic response was seen, probably because of poor compliance. The patient was known to be hypersensitive to abacavir, but no kidney disorder had been documented. Since November 2001, the patient had been receiving only chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ). During that time, the patient reported regularly to our outpatient clinic and seemed to be compliant with TMP-SMZ therapy. He wanted to start a new antiretroviral treatment regimen in February 2002. At that time, the patient had a CD4 T cell count of 80 cells/μL in whole blood, an HIV load of 2 million copies/mL, and a serum creatinine level of 69 μmol/L. The patient started receiving therapy with lamivudine (150 mg b.i.d.), stavudine (40 mg b.i.d.), lopinavir-ritonavir (400/100 mg b.i.d.), and tenofovir (300 mg q.d.). Two and 4 weeks later, the serum creatinine level increased to 100 and 134 μmol/L, respectively.

Eight weeks after the initiation of antiretroviral therapy, the patient presented with fever, diarrhea, and malaise. He had stopped taking all medication 2 days earlier. No clinical signs of dehydration were found. Blood pressure was 120/80 mm Hg, the creatinine level was 310 μmol/L, the uric acid level was 307 μmol/L, and the blood urea nitrogen level was 17.7 mmol/L; serum C-reactive protein, serum potassium, sodium, and phosphate levels were within normal limits. Base excess was −6.1 mmol/L, the serum bicarbonate level was 20 mmol/L, and pH was 7.40 with an anion gap of 5 mmol/L. The urinary sodium level was 94 mmol/L, with a fractional sodium excretion of 3.2%. Urinalysis revealed no glycosuria and 5–10 WBCs per high-power field. Urine protein analysis revealed mild, mixed proteinuria (protein level, 0.72 g/L) with an increased IgG level (69 mg/g creatinine). Because the plasma HIV load was 6800 copies/mL and the CD4 T cell count was 240 cells/μL, poor compliance was not suspected. The results of serum PCR for CMV and Epstein-Barr virus (EBV), serological tests for Hantavirus, and tests for antinuclear antibodies, antineutrophil cytoplasm antibody, and cryoglobulin were negative. The findings of renal sonography were normal. Stool cultures remained sterile.

Examination of renal biopsy specimens revealed a mild interstitial infiltrate consisting of lymphocytes, focal atrophic changes in ~10% of cortical tubules and luminal ectasia and loss of brush border in other tubules. Glomeruli appeared normal. Immunofluorescence of stained glomerular and interstitial specimens did not reveal IgG, IgM, IgA, fibrinogen/fibrin, or C3. No evidence of infection, including toxoplasmosis, CMV infection, and EBV infection, was seen. Electron microscopy showed no glomerular ultrastructural abnormalities.

Serum creatinine levels slowly decreased during the month.
after the patient stopped taking medication (figure 1). In October 2002 (6 months later), the patient was receiving only TMP-SMZ. The creatinine level was 139 μmol/L, and mild tubular proteinuria was still present (protein level, 0.25 g/L; α1-microglobulin level, 196 mg/g creatinine; and albumin level, 20 mg/g creatinine). Urinalysis showed no WBCs or RBCs. The HIV load was 2,390,000 copies/mL, and the CD4 T cell count was 80 cells/μL. The patient again started therapy with lamivudine (150 mg b.i.d.), stavudine (40 mg b.i.d.), and lopinavir-ritonavir (400/100 mg b.i.d.) but not tenofovir. In January 2003, the CD4 T cell count was 220 cells/μL, the HIV load was 6600 copies/mL, and the creatinine level was 101 μmol/L. No signs of renal deterioration were found (figure 1).

**Discussion.** The safety profile of tenofovir was reported to be similar to placebo in a clinical study involving 189 patients [8], although adefovir and cidofovir are associated with considerable renal toxicity [1–3]. In this case report, there are several arguments that tenofovir treatment was associated with the development of acute renal failure. First, there was a close relationship between administration of tenofovir and clinical deterioration. After stopping treatment, renal dysfunction quickly improved. Starting the same treatment without tenofovir did not cause any side effects. Second, the proximal tubular atrophy without evidence of glomerulonephritis that occurred in our patient resembled adefovir-associated nephrotoxicity [1] and tenofovir-associated nephrotoxicity described in 1 patient by Verhelst et al. [4]. Our patient had tubular dysfunction associated with mild acidosis due to bicarbonate loss, but the features of Fanconi syndrome and diabetes insipidus reported by Verhelst et al. [4] were absent. Third, coadministration of lopinavir-ritonavir is known to increase the maximum concentration and the area under the curve for tenofovir by ~30% [9]. Despite there being weaker tubular cell cytotoxicity associated with tenofovir use (compared with cidofovir use) in cell culture [10], animal exposure levels (based on areas under the curve) of 2–20 times higher than those observed in humans after administration of tenofovir (300 mg q.d.) caused renal tubular toxicity after 56 days to 42 weeks of treatment [9]. Increased tenofovir exposure caused by drug interaction may have increased the chance of renal toxicity in our patient.

It seems unlikely that other drugs were responsible for acute renal failure in our patient, because therapy with all of the other drugs was restarted without effect on renal function. Immune restoration syndrome, a result of inflammation caused by an exuberant response of the reconstituted immune system to pre-existing or subclinical infections caused by opportunistic pathogens [11], is unlikely, because this syndrome is not known to be associated to renal insufficiency, because microbial antigens were not detected in serum or renal biopsy specimens, and because the second treatment regimen did not cause renal failure, despite comparable virological and immunological responses to antiretroviral therapy. HIV-associated nephritis also seems unlikely, because typical histological features with focal segmental

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**Figure 1.** Serum creatinine levels and HIV loads in a patient with AIDS during an antiretroviral treatment regimen that included tenofovir (TDF; lamivudine [3TC], 150 mg b.i.d.; stavudine [d4T], 40 mg b.i.d.; lopinavir-ritonavir [LOP/rit], 400/100 mg b.i.d.; and TDF, 300 mg q.d.) and during a subsequent antiretroviral treatment regimen that did not include TDF (3TC, 150 mg b.i.d.; d4T, 40 mg b.i.d.; and LOP/rit, 400/100 mg b.i.d.). Dates are shown as day, month, and year.
glomerulosclerosis were not seen, and because the decrease in the HIV load that occurred during antiretroviral treatment paralleled the deterioration of renal function. Finally, hepatitis C–associated hepatorenal syndrome is unlikely, because no clinical or laboratory signs of liver cirrhosis were present and increased fractional sodium excretion was found. Cryoglobulin-associated vasculitis was not found during histological examination, and no cryoglobulin was found in serum.

In conclusion, in our opinion, our patient developed acute tubular necrosis due to tenofovir exposure. This case report suggests that tenofovir might be toxic for proximal tubular cells, but the risk seems to be much lower than that associated with use of cidofovir or adefovir. Clinicians should be aware of possible drug interactions, because increased tenofovir exposure due to coadministration of lopinavir-ritonavir could have contributed to toxicity. Pharmacological studies should evaluate the interaction that other ritonavir-containing antiretroviral therapies have on tenofovir levels. Monitoring of creatinine levels should be performed in patients taking tenofovir during at least the first 2 months of treatment, especially when drug combinations known to increase tenofovir exposure are used. The reasons for individual susceptibility to tenofovir remain to be elucidated.

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References