

## Tenofovir-Related Nephrotoxicity in Human Immunodeficiency Virus–Infected Patients: Three Cases of Renal Failure, Fanconi Syndrome, and Nephrogenic Diabetes Insipidus

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**We report 3 cases of renal toxicity associated with use of the antiviral agent tenofovir. Renal failure, proximal tubular dysfunction, and nephrogenic diabetes insipidus were observed, and, in 2 cases, renal biopsy revealed severe tubular necrosis with characteristic nuclear changes. Patients receiving tenofovir must be monitored closely for early signs of tubulopathy (glycosuria, acidosis, mild increase in the plasma creatinine level, and proteinuria).**

The rapid development of antiviral drugs has allowed considerable reduction in mortality and morbidity in HIV-infected patients. However, some of these newly introduced antiviral drugs, such as indinavir, didanosine, and zalcitabine, have been associated with potentially serious nephrotoxicity. Two nucleotide analogues, didanosine and zalcitabine, have been found to be responsible for proximal renal tubular dysfunction and acute renal failure [1–3]. Nephrotoxic effects have also been described in association with other drugs received by HIV-infected patients, such as indinavir, which can cause nephrolithiasis and intratubular crystallization [4, 5], and foscarnet, which has been found to be responsible for direct injury to tubular cells and formation of crystals in the glomerular capillaries [6]. In some patients, such nephrotoxicity can lead to definitive renal failure.

Tenofovir disoproxil fumarate (DF), a tenofovir prodrug, is a new and promising nucleotide analogue with proven activity

against HIV reverse transcriptase that was recently approved by the US Food and Drug Administration. A recent placebo-controlled, phase III trial showed that this drug has a favorable safety profile and good antiviral activity against drug-resistant strains of HIV [7]. Although preliminary animal studies have shown that nephrotoxicity is the dose-limiting toxicity, to date, clinical studies have not reported severe nephrotoxicity in patients with normal baseline renal function who were treated for several months with tenofovir at a dosage of 300 mg once daily (unpublished investigator brochure, Gilead Science). To date, ~160 HIV-infected patients have been treated at Hôpital Saint-Louis (Paris, France) with this new antiviral agent. Herein, we report 3 cases of nephropathy secondary to tenofovir use.

All 3 affected patients had a long medical history of HIV infection (2 patients had HIV infection diagnosed in 1987, and 1 had it diagnosed in 1998) and had received different courses of antiretroviral therapies before they began receiving tenofovir. When tenofovir therapy was started, the CD4 cell count was <50 cells/mm<sup>3</sup> in these 3 patients. Tenofovir DF (300 mg per day) was given orally in combination with other antiviral agents considered to have no renal side effects (table 1). None of the patients had evidence of previous nephropathy or serious renal function impairment: they had serum creatinine levels of <1.20 mg/dL, and proteinuria was not detected. No other drugs that interfere with renal function (such as adefovir or didanosine) were given, except for ramipril, which was prescribed to 1 patient for prior hypertension. A slight increase in the serum creatinine level (<1.6 mg/dL) was observed in all 3 patients a few weeks after initiation of tenofovir therapy, but therapy with this drug was not interrupted at that time.

Two of the patients were admitted to Hôpital Saint-Louis several months after the initiation of tenofovir therapy because of a rapid decline in renal function, with peak creatinine levels of 688  $\mu$ M (7.80 mg/dL) in one patient and 240  $\mu$ M (2.71 mg/dL) in the other. Renal failure was not due to use of other medications, rhabdomyolysis, or hemodynamic instability could not explain this renal failure. In both patients, striking hypokalemia with elevated urine potassium excretion, metabolic acidosis with normal anion gap, and important hypophosphoremia were noted. Urinalysis revealed tubular proteinuria and leukocyturia, with no hematuria, eosinophiluria, or bacteriuria. A kidney biopsy was performed for these 2 patients. Histologic examination of the biopsy specimen (figure 1) revealed severe acute tubular necrosis associated with marked interstitial fibro-edema. Distal and prox-

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**Table 1. Characteristics of and clinical data for 3 HIV-infected patients with tenofovir-related nephrotoxicity.**

Patient	Age, years	Antiretroviral drugs received	Duration of tenofovir treatment, months	Serum creatinine level, mg/dL		Acidosis hypokalemia present	Glucosuria present	Diabetes insipidus present	Renal biopsy performed
				Baseline	Peak				
1	55	Lopinavir-ritonavir, abacavir	7	0.91	7.80	Yes	Yes	No	Yes
2	31	Didanosine, lamivudine, ritonavir, amprenavir, T20	6	0.93	1.74	No	Yes	Yes	No
3	42	Lamivudine, abacavir, lopinavir-ritonavir	11	1.15	2.71	Yes	No	No	Yes

imal renal tubules were equally affected by severe epithelial lesions. Dystrophic cells with large, abnormal nuclei (i.e., karyomegaly) were noted, predominantly in proximal tubules. Presence of large vacuoles related to hypokalemia were also observed in proximal tubular cells. Glomeruli and blood vessels appeared normal. No tubular crystals were observed when fresh tissue samples were examined by polarized light microscopy. No signs of BK virus nephritis or HIV-associated nephropathy were detected. Immunofluorescence tests revealed the absence of immunoglobulins and of complement deposits in the renal tissue. Discontinuation of all antiretroviral therapy was associated with improvement of renal function and rapid (<2 weeks) normalization of proteinuria, leukocyturia, hypophosphatemia, acidosis, and hypokalemia. No follow-up biopsies were performed for either of these patients. However, the serum creatinine level remained elevated in both patients (190  $\mu$ M [2.14 mg/dL] in one patient, and 150  $\mu$ M [1.69 mg/dL] in the other), indicating that there was partially irreversible renal damage, which could be explained by the importance of the fibrotic lesions noted during the initial examinations of the biopsy specimens. All antiretroviral agents other than tenofovir were reintroduced a few weeks after discontinuation of tenofovir therapy, and there were no new increases in the serum creatinine level or recurrences of tubular dysfunction.

For the third patient, the major side effect of tenofovir use was severe polyuro-polydipsic syndrome (i.e., daily urine output of >6 L), which started 6 months after initiation of tenofovir treatment. A water deprivation test confirmed the presence of nephrogenic diabetes insipidus by revealing rapid weight loss, elevation of plasma osmolality, stability of urine output (>250 mL/h), and no increase in urine osmolality (117 mOsm/kg H<sub>2</sub>O), despite an increase in the plasma antidiuretic hormone level (4.90 pg/mL). Proteinuria was detected (protein excretion rate, 1.24 g per 24 h), as was normoglycemic glucosuria, but the patient did not undergo renal biopsy, because the renal impairment was transient and mild (serum creatinine level, 154  $\mu$ M [1.74 mg/dL]). All signs of tubulopathy resolved 3 weeks after tenofovir therapy alone was discontinued. This observation suggests that tenofovir is potentially toxic not only for the

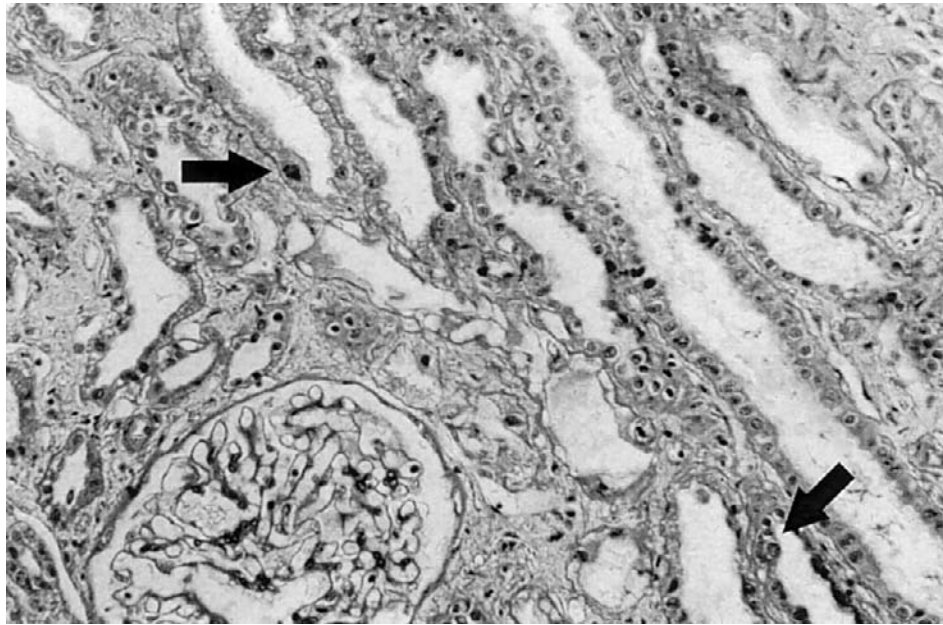
proximal tubule but also for epithelial cells of the collecting duct.

These 3 patients are among the first reported to have presented with severe renal failure involving tubular dysfunction (Fanconi syndrome) that was probably associated with tenofovir therapy. Four main arguments strongly suggest a link between tenofovir use and these renal effects.

1. Most laboratory values returned to normal ranges after tenofovir use was discontinued, and the abnormalities did not recur when therapy with other antiviral drugs was reintroduced.

2. Nephrotoxicity involving renal failure, proteinuria, and renal tubular dysfunction with Fanconi syndrome has already been noted in toxicological studies. Renal side effects were even considered to be the dose-limiting toxicity in animal studies. Histopathological findings for the kidneys of animals (including monkeys) that received high doses of tenofovir included tubular cell karyomegaly, tubular cell degeneration, and necrosis, as well as interstitial nephritis. The incidence, severity, and reversibility of clinical and histological abnormalities are known to be related to the dose and duration of treatment (unpublished investigator brochure, Gilead Science). These pathological findings are very similar to those we observed in the 2 patients who underwent kidney biopsy (figure 1).

3. Other nucleotide analogues, such as cidofovir and adefovir, have recently been associated with renal failure, diabetes insipidus, and proximal renal tubular dysfunction [1–3]. Renal toxicity is mediated by proximal tubule epithelial cells that express human renal organic anion transporter 1 (hOAT1) and actively uptake these drugs [8]. Cidofovir-associated nephrotoxicity can be reduced when probenecid (an hOAT1 inhibitor) is given concurrently. This organ-specific membrane transporter has also been shown to mediate uptake of tenofovir by epithelial cells, although no particular cytotoxicity is noted in vitro when Chinese hamster ovary cells expressing hOAT1 are in the presence of tenofovir [9]. Although adefovir, which is structurally close to tenofovir, may cause acute tubular necrosis by direct mitochondrial toxicity [10], tenofovir does not seem



**Figure 1.** Masson stain of a renal biopsy sample obtained from patient 1 showing severe tubular necrosis with dystrophic epithelial cell nuclei (arrows) and interstitial fibro-edema.

to interfere with mitochondrial function, compared with other nucleoside reverse-transcriptase inhibitors [11].

4. Verhelst et al. [12] recently reported a similar case of nephrotoxicity in a patient who presented with acute renal failure, Fanconi syndrome, and diabetes insipidus related to tenofovir treatment.

The reason these 3 patients developed renal dysfunction remains unclear. Because the primary route of elimination of tenofovir is via the urine, one can hypothesize that drugs that interfere with its renal excretion can lead to accumulation of tenofovir. Because nephrotoxicity seems to be dose-dependent in animal models, dose-dependency may be one of the potential mechanisms of tenofovir-associated adverse events. It has been shown that lopinavir-ritonavir can increase plasma concentrations and the area under the concentration-time curve of tenofovir by 30% (unpublished investigator brochure, Gilead Science). Of interest, 2 of our patients were receiving the combination of lopinavir-ritonavir and tenofovir.

In conclusion, we would like to emphasize the possible role that tenofovir plays in inducing renal failure or tubular dysfunction in HIV-infected patients. Although nephrotoxicity certainly occurs much less frequently with tenofovir than it does with other nucleotide analogues, such as cidofovir or adefovir, use of tenofovir by patients with mild renal dysfunction and/or use for longer durations might be associated with renal toxicity, as suggested by animal studies. Patients receiving tenofovir must be monitored closely for early signs of tubulopathy (i.e., glycosuria, acidosis, mild increase in plasma creatinine

levels, and proteinuria), even several months after the initiation of treatment; if there are signs of tubulopathy, therapy should be stopped as soon as possible to avoid the risk of definitive renal failure.

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