Fatal Lactic Acidosis and Acute Renal Failure after Addition of Tenofovir to an Antiretroviral Regimen Containing Didanosine

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We describe a 49-year-old man with human immunodeficiency virus infection and stable chronic renal insufficiency who developed acute oliguric renal failure and severe lactic acidosis and who died several weeks after tenofovir was added to an antiretroviral regimen that included didanosine. Although the role of tenofovir in precipitating acute renal failure is unclear, progressive accumulation of the drug and pharmacologic interaction that caused increased levels of didanosine were the likely antecedents of increased mitochondrial toxicity that led to lactic acidosis.

Tenofovir is a nucleotide analogue of adenosine 5′-monophosphate that was approved for the treatment of HIV infection in October 2001. In a 48-week, randomized, double-blind study [1], intensification of antiretroviral regimens with the addition of tenofovir resulted in durable reductions in the HIV load. The safety profile of tenofovir during the study was similar to that of placebo. However, in the Viread (tenofovir) package insert [2], Gilead Sciences recommends that, because tenofovir is mainly eliminated by the kidney, it should not be given to patients with renal insufficiency (as evidenced by a creatinine clearance <60 mL/min). Gilead Sciences also describes a drug-drug interaction between tenofovir and didanosine, the mechanism of which is poorly understood, that results in increased didanosine levels. Thus, they recommend that, if the 2 drugs are to be administered concomitantly, tenofovir should be taken 2 h before or 1 h after didanosine.

We describe a 49-year-old man who was known to have had AIDS since 1987 and a CD4 cell count of <100 cells/μL since 1995. His medical history was also notable for adrenal insufficiency, hypogonadism, anemia, peripheral neuropathy, asthma, and large B cell lymphoma of the thoracic spine, which was believed to be in remission after the patient underwent chemotherapy and radiation therapy. The patient had been receiving multiple antiretroviral drugs and was infected with multidrug-resistant HIV, as determined on the basis of several reverse-transcriptase (41L, 74V, 103N, 184V, 210W, and 215Y) and protease (36I, 54V, 71V, 82A, and 90M) mutations noted by genotypic resistance testing. His most recent circulating HIV load was 1100 copies/mL, and his most recent CD4 cell count was 35 cells/μL. Seven weeks before admission to the hospital, his antiretroviral regimen was changed from didanosine, efavirenz, saquinavir, and ritonavir to didanosine, tenofovir, amprenavir, and ritonavir.

Case report. The patient was known to have had mild renal insufficiency since 1996; during the year before admission to the hospital, his serum creatinine level had ranged from 1.9 to 2.8 mg/dL, and it was 2.3 mg/dL just before he started receiving tenofovir (estimated creatinine clearance, 41 mL/min). The patient had received didanosine in its original buffered formulation for almost 3 years before switching to the new enteric-coated didanosine formulation (400 mg/day) several months before tenofovir therapy was started. This didanosine dosage was higher than the 200 mg/day recommended for a creatinine clearance of 30–59 mL/min and, therefore, could have resulted in a higher concentration of didanosine. The patient and provider discussed the risks of renal and pancreatic toxicity associated with the new regimen versus the possible virologic benefits, and they decided to proceed. The patient was instructed to take didanosine and tenofovir 12 h apart.

The patient returned for a follow-up visit 2 weeks after he started the new regimen, at which time he was tolerating the new regimen well; the creatinine level at this time was 2.0 mg/dL (HCO₃⁻ level, 21 mM). He was also given 40-mg tablets of furosemide to be used, as needed, up to twice per day for lower-extremity edema, which was believed to be related to hydrocortisone therapy (30 mg q.d.) for adrenal insufficiency, as well as his low albumin level (3.0 g/dL). The patient returned for a follow-up appointment 2 weeks later with persistent edema, and furosemide was switched to bumetanide (2 mg up to twice per day). At this visit, the patient complained of increased lower-extremity pain, which, at the time, was attributed to edema; however, in retrospect, the pain was more likely a result...
of worsening neuropathy. Within a week, the edema markedly improved while the patient was receiving bumetanide.

Two weeks after the previous clinic visit, the patient was brought to the emergency department with a 4-day history of progressive fatigue, weakness, confusion, oliguria, and myalgia and an increase in his peripheral neuropathic pain, compared with the typical intensity and frequency of pain in lower extremities that had been attributed to peripheral neuropathy during the prior year. At admission to the emergency department, the patient was noted to be hypotensive (blood pressure, 90/50 mm Hg), and laboratory studies revealed a blood urea nitrogen level of 78 mg/dL, a creatinine level of 7.6 mg/dL, and an arterial blood gas pH of 6.93, with an HCO$_3^-$ level of 5 mM. The patient was transferred to the intensive care unit and began undergoing continuous venovenous hemofiltration (CVVH) and receiving medicine to maintain blood pressure (norepinephrine), and he subsequently underwent intubation. All antiretroviral therapy was discontinued. His lactic acid level, which was 5.5 mM (normal range in plasma, 0.5–2.2 mM) at the time of admission, increased to a maximum of 16.7 mM on hospital day 3, despite the patient’s undergoing daily CVVH with a 5% bicarbonate drip at a rate of up to 150 mL/h (35 mM of bicarbonate was also added to the hemofiltration replacement fluid shortly thereafter).

Abdominal/pelvic CT, bronchoscopy, blood cultures, and paracentesis were all performed within the first 72 h after admission to determine whether infection was the cause of the patient’s hemodynamic instability and lactic acidosis. No evidence of infection was found, and the patient remained afebrile. Nevertheless, broad-spectrum antibiotics (vancomycin and meropenem) were given during the patient’s hospital course. Because lactic acid consists of small molecules that are continually removed by CVVH, the nephrologist indicated that, in the absence of evidence of ongoing infection, the continuing increase in lactic acid levels (despite the performance of CVVH) was most likely associated with a toxin (i.e., tenofovir and/or didanosine) with a large volume of distribution that was not easily removed by ultrafiltration.

In light of the severe lactic acidosis, riboflavin was added to the patient’s medication regimen on hospital day 3, and carnitine and thiamine were added on hospital day 4. With continued CVVH and bicarbonate infusions, the lactic acidosis gradually reversed to a near normal lactic acid value of 2.3 mM by hospital day 7, only to rebound to 8.1 mM 2 days later when the bicarbonate drip was decreased to 10 mL/h during CVVH. The lipase level was noted to be 377 U/L (normal range, 22–51 U/L) at the time of admission to the hospital, but it rapidly improved with discontinuation of antiretroviral therapy. While the patient was undergoing CVVH, his serum creatinine level had decreased to 2 mg/dL by hospital day 5, but, on that day, a renal scan revealed bilateral hypofunction with no tubular excretion of tracer, consistent with severe acute tubular necrosis. On hospital day 12, CVVH was stopped, and the lactic acid and creatinine levels again started to increase, suggesting persistent mitochondrial toxicity and renal failure. The following day, a family conference was held, at which time the patient’s partner and family members expressed the patient’s prior wish not to undergo prolonged aggressive therapy, as evidenced by his living will. After intensive care was withdrawn, the patient was discharged to home with hospice, and he subsequently died.

**Discussion.** Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Administration of tenofovir to rats, dogs, and monkeys at supratherapeutic doses as part of toxicology studies resulted in renal toxicity. Increases in the serum creatinine level, the blood urea nitrogen level, and urine levels of glucose, protein, phosphates, and/or calcium were observed to varying degrees in 4 animal species [2]. Consequently, all patients with a creatinine clearance of <60 mL/min and/or a serum creatinine level of >1.5 mg/dL were excluded from the phase 1/2 clinical trials of this drug [3]. There is no information from clinical trials to estimate the frequency of or consequences associated with tenofovir nephrotoxicity at a baseline estimated creatinine clearance of 41 mL/min, as occurred in our patient. Of the 687 patients from the 2 randomized, placebo-controlled studies GS-98–902 (phase 2) [1, 4] and GS-99–907 (phase 3) [4] who received tenofovir, none discontinued the study because of tenofovir-related serum creatinine elevations or hypophosphatemia. However, 5% of patients did have an increase in their serum creatinine level of >0.5 mg/dL over their baseline level, but these increases were generally transient and never reached a level of ≥2.1 mg/dL. Seven (1%) of the 687 patients developed lactic acidosis. No cases of lactic acidosis were seen in the placebo group, and all patients who developed lactic acidosis were also concomitantly receiving stavudine or didanosine [4].

Symptomatic lactic acidosis in HIV-infected patients is known to be associated with extensive exposure to nucleoside reverse-transcriptase inhibitors (NRTIs) and can be fatal. In a retrospective analysis of 12 HIV-infected patients admitted to a university hospital or a Veterans Affairs hospital in Birmingham, Alabama, with symptomatic lactic acidosis syndrome, 5 (42%) were reported to have died after experiencing rapid progression to multiple-organ failure [5]. In this study, the most common NRTI components of the 12 patients’ antiretroviral regimens were stavudine and didanosine. The Swiss HIV Cohort Study looked at the prevalence of and risk factors for hyperlactatemia in 880 patients receiving antiretrovirals during a 1-month period and found that the 73 patients (8.3%) who presented with hyperlactatemia were more likely to have been receiving stavudine [6].

NRTI-associated lactic acidosis is believed to be a consequence of the drug’s toxic effect on the mitochondria in liver...
and skeletal muscle cells. Cihlar et al. [7] determined the in vitro cytotoxicity of tenofovir compared with other NRTIs. Exponentially growing human liver cells (hepatoblastoma-HEPG2 cells) and human skeletal muscle cells were incubated in the presence of the NRTIs in question for 8 and 6 days, respectively, and cytotoxicity values were determined using neutral red–based spectrophotometric assay. Among all the NRTIs tested, zalcitabine was the most cytotoxic and lamivudine was the least cytotoxic to the HEPG2 liver cells, with the order of toxicity as follows (the operators refer to the degree of toxicity/ inhibition, compared with other drugs; “>” denotes a higher magnitude of difference): zalcitabine > zidovudine > stavudine > abacavir > didanosine > tenofovir > lamivudine. Among all the NRTIs tested, stavudine was the most cytotoxic and lamivudine was the least cytotoxic to the skeletal muscle cells, with the order of toxicity as follows: stavudine > zalcitabine > abacavir > zidovudine > didanosine > tenofovir > lamivudine. Additionally, the in vitro growth of renal proximal tubule epithelial cells was shown to be only marginally affected by tenofovir. This same group also examined mitochondrial DNA levels in HEPG2 cells, skeletal muscle cells, and renal proximal tubule epithelial cells [8]. They found that mitochondrial DNA synthesis was inhibited most by zalcitabine and least by abacavir, tenofovir, and lamivudine, with the following order of inhibition: zalcitabine > didanosine > stavudine > zidovudine > abacavir = tenofovir = lamivudine. In addition, they measured lactic acid production by the HEPG2 cells and skeletal muscle cells in response to the NRTIs and found that zidovudine doubled the amount of extracellular lactate produced, compared with the baseline level. Tenofovir and lamivudine had little effect on lactate production, and zalcitabine only produced a marginal increase (abacavir, didanosine, and stavudine were not tested).

The low potential for mitochondrial toxicity associated with use of tenofovir alone may be accounted for by the fact that its pyrophosphate metabolite inhibits HIV-1 reverse transcriptase at concentrations much lower than those needed to inhibit nuclear DNA polymerases or mitochondrial polymerase γ [9, 10]. Didanosine, on the other hand, has been associated with mitochondrial toxicity at therapeutic doses [11]. Prior work has also shown that the mitochondrial toxicity of zalcitabine, stavudine, and didanosine is concentration dependent [12]. Foli et al. [11] used a cytofluorimetric technique to predict the mitochondria-dependent pancreatic toxicity of didanosine alone or in combination with hydroxyurea. They found that even though hydroxyurea alone did not alter mitochondrial function, when added to high (but not low) concentrations of didanosine, it did increase mitochondrial toxicity in the pancreatic cell line. The authors speculate that this is due to the fact that mitochondrial dysfunction becomes evident only when ATP production decreases to less than a certain threshold. Thus, they conclude that “a relatively small increase in didanosine concentration in the critical range could have a dramatic effect on mitochondrial functionality” [11, p. 1692]. This may explain the profound lactic acidosis seen in the aforementioned patient, because, when didanosine is administered with tenofovir, the area under the curve for didanosine increases by a mean of 44% [2]. In keeping with the recommendation that tenofovir be taken 2 h before or 1 h after administration of didanosine [2], our patient had been instructed to take didanosine with his morning medications and tenofovir with his evening medications. However, given that didanosine is partially renally excreted as well, a separation of even 12 h may not have been sufficient, considering the patient’s degree of renal insufficiency.

Factors that contributed to this patient’s acute renal failure and lactic acidosis include his preexisting renal insufficiency, his use of diuretics (furosemide and bumetanide), and the concomitant administration of tenofovir and didanosine. The worsening renal function probably resulted in the accumulation of both tenofovir and didanosine. The increased tenofovir levels likely increased the already high concentration of didanosine, which, in turn, led to mitochondrial toxicity, as manifested by lactic acidosis. At some point, the level of tenofovir may have been high enough to cause direct nephrotoxicity, comparable to that seen in the early tenofovir toxicology studies performed with animals.

In conclusion, this case suggests that the administration of tenofovir and, particularly, the coadministration of didanosine with tenofovir should be undertaken with caution in patients who have renal insufficiency, even if it seems to be mild and stable.

References

7. Cihlar T, Birkus G, Greenwalt DE, Hitchcock MJM. Tenofovir exhibits low cytotoxicity in various human cell types: comparison with other