The availability of highly active antiretroviral therapy has improved the survival and quality of life of patients infected with HIV. Clinicians are now focusing on the management of metabolic complications and previously unrecognized drug toxicities. The incidence and prevalence of kidney disease are increasing in older HIV-infected patients because of the widespread use of antiretroviral therapy.

The introduction of highly active antiretroviral therapy has also been associated with drug-related renal complications, such as nephrolithiasis with the protease inhibitor indinavir and Fanconi syndrome with the NRTI tenofovir disoproxil fumarate. Although the data are controversial, tenofovir has also been associated with cumulative effects when combined with didanosine or a protease inhibitor. These uncommon yet serious complications pose a challenge to clinicians to manage them early after antiretroviral therapy has been initiated. We present the cases of 3 HIV-infected patients who have proximal tubular dysfunction and nephrogenic diabetes insipidus and who have been exposed to an antiretroviral regimen containing tenofovir and didanosine. In addition, we discuss the pathophysiological hypotheses that have been proposed in the medical literature and their clinical implications.

CASE SUMMARIES

Patient 1
A 32-year-old man presented with a 4- to 6-week history of nausea, vomiting, and excessive thirst and urination. He received a diagnosis of HIV infection in 1996 and has had AIDS since 2001, when cerebral toxoplasmosis was diagnosed. He had been drinking ten 20-oz bottles of water per day and voided hourly. Furthermore, he reported a 20-lb weight loss throughout this period. His antiretroviral therapy regimen included tenofovir, didanosine (250 mg/d), and efavirenz. Physic
Physical examination showed an ill and debilitated man with dry mucous membranes. On admission, his urinary output had been 2.2 L in 4 hours. Otherwise, findings from the examination were unremarkable.

Admission laboratory studies were obtained. The Table shows the laboratory results, which included an anion gap of 14 (normal, 9 to 15). The laboratory test results suggested proximal tubular damage consistent with Fanconi syndrome—specifically, hyperchloremic, nonanion gap metabolic acidosis; hypouricemia; hypophosphatemia; and normoglycemic glycosuria. A water deprivation test was performed (Figure) and showed that the patient did not respond to 2 μg (4 μg/mL) of desmopressin. No improvement in urinary concentrating ability was noted despite desmopressin administration; thus, the results were highly suggestive of nephrogenic diabetes insipidus. The patient’s antiretroviral therapy was discontinued, and he received intravenous hydration. His symptoms and laboratory results improved. He was seen as an outpatient, during which his antiretroviral therapy was changed to the abacavir/lamivudine coformulation plus lopinavir/ritonavir. His symptoms and the abnormalities in his laboratory results were improved at his 2-month follow-up visit.
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Figure. Water deprivation test results consistent with nephrogenic diabetes insipidus. Data from Patient 1. Vertical line at 1 pm represents the time desmopressin acetate was given. Figure also shows results of a hypothesized patient who has a normal water deprivation test result and one who has central diabetes insipidus. Serum sodium levels were monitored hourly and did not change considerably during the test.

**Patient 2**
A 39-year-old man presented with a 70-lb weight loss over 8 to 9 months, which was accompanied by nausea and excessive thirst and urination. He had received a diagnosis of HIV infection in the early 1990s, when he presented with pneumococcal pneumonia. He also had hepatitis C, presumably a consequence of receiving numerous blood transfusions after a near-drowning episode complicated by anoxic brain injury, tracheostomy, and prolonged hospitalization. On admission, his antiretroviral therapy included tenofovir, didanosine (250 mg/d), and lopinavir/ritonavir. His initial didanosine dosage was 400 mg/d, but it had been decreased in March 2004 because of weight loss. However, he continued to lose weight and was admitted in September 2004 for evaluation of a 70-lb weight loss over 8 to 9 months.

Physical examination showed a cachectic man in no acute distress with a tracheostomy scar and dry mucous membranes. Findings from the rest of the examination were unremarkable. Initial laboratory test results were obtained (Table), which included an anion gap of 13. Urine was collected for analysis of amino acids; marked generalized aminoaciduria was indicated. The presence of hyperchloremic, non-anion gap metabolic acidosis; hypouricemia; hypophosphatemia; and aminoaciduria was consistent with Fanconi syndrome. In addition, the patient’s history of polydipsia, polyuria, and low urinary osmolality was consistent with nephrogenic diabetes insipidus.

Given the clinical scenario and laboratory abnormalities, it was deduced that both the syndrome and the diabetes insipidus were related to tenofovir use. The patient's antiretroviral therapy was discontinued, and he received intravenous hydration. His antiretroviral therapy was restarted but with tenofovir being replaced with the abacavir/lamivudine coformulation. At the 2-month follow-up visit, his electrolyte abnormalities and clinical symptoms had resolved.

**Patient 3**
A 38-year-old man presented with a 5-month history of a 10-lb weight loss, wasting, nausea, vomiting, and anorexia. He had been drinking approximately ten 20-oz bottles of water per day. The patient had received a diagnosis of HIV infection in 1996 and also had hepatitis B. His antiretroviral therapy included ritonavir-boosted fosamprenavir, tenofovir, and didanosine (250 mg/d). Physical examination showed a thin, ill-appearing, cachectic man with dry mucous membranes. Urinary output at admission was 3.6 L in 8 hours. Findings from the rest of the physical examination were
unremarkable.
Results of admission laboratory tests are shown in the Table. Laboratory test results showed an anion gap of 14. Hyperchloremic, non-anion gap metabolic acidosis; hypouricemia; hypophosphatemia; and glycosuria were present. These findings were interpreted as being consistent with Fanconi syndrome. The low urine osmolality and the history of polydipsia and polyuria were highly suggestive of diabetes insipidus, presumably a nephrogenic type, assumed to be related to tenofovir use. The patient's antiretroviral therapy was discontinued, and he received bicarbonate replacement therapy. After discontinuation of antiretroviral therapy, his electrolyte abnormalities and clinical symptoms were improved at his 2-month follow-up visit. To date, he has not needed antiretroviral therapy.

DISCUSSION
Fanconi syndrome and nephrogenic diabetes insipidus are uncommon complications that have been associated with the use of tenofovir.\(^1\)\(^-\)\(^3\) Fanconi syndrome presents with proximal tubular dysfunction. The proximal tubule is responsible for most of the reabsorption of sodium, bicarbonate, phosphorus, lactate, amino acids, glucose, and citrate. Proximal tubular dysfunction leads to acidosis from defective bicarbonate reabsorption and hyperchloremia. Elevated chloride and low bicarbonate levels do not cause a net increase of cations; thus, the anion gap—calculated here by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentration of sodium (cation)—continues to be normal.\(^7\) It also causes normoglycemic glycosuria, low-molecular-weight proteinuria, aminoaciduria, and hypophosphatemia with hyperphosphaturia that may lead to rickets or osteomalacia. The presence of hypercalciuria and hypokalemia may lead to polyuria or nephrolithiasis, or both.

Fanconi syndrome is commonly seen in children as a congenital disorder; however, in adults it is typically an acquired disorder. Common acquired causes are multiple myeloma; heavy metal intoxication; and the use of certain medications, including cisplatin, ifosfamide, valproate, aminoglycosides, cidofovir, adenosin diphosphokinase, and tenofovir.

Diabetes insipidus is characterized by polyuria and polydipsia. Its 2 main types are central and nephrogenic. Central diabetes insipidus is associated with head trauma, intracranial neoplasm, and infiltrative disorders (eg, sarcoidosis). Its pathophysiology is driven by a low level or absence of antidiuretic hormone (ADH). The main function of ADH is to increase water permeability in the late distal tubule and collecting duct by incorporating water channels into the apical membrane of the collecting duct cells.

Nephrogenic diabetes insipidus can be genetic because of ADH receptor mutations that produce various degrees of renal insensitivity to ADH. It can also be associated with the use of certain medications (eg, lithium carbonate, demeclocycline hydrochloride; amphotericin B, ifosfamide, cidofovir, tenofovir, didanosine, foscarinet sodium), hypokalemia, hypercalcemia, urinary tract obstruction, sickle cell disease or trait, amyloidosis, Sjogren syndrome, and pregnancy.

Most of the time, diabetes insipidus is a clinical diagnosis with laboratory confirmation. A typical laboratory finding is a urine specific gravity of less than 1.005 or a urine osmolarity of less than 200 mOsm/kg H\(_2\)O.\(^8\) In patients with diabetes insipidus and no cognitive impairment, hypernatremia is not present because as the excessive water excretion stimulates thirst, the water loss is equalized with increased water consumption. However, any interruption of the thirst mechanism will produce hypernatremia.

Diabetes insipidus can be differentiated with a water deprivation test (Figure). After a 24-hour water deprivation test and hourly monitoring of urinary output, urine and plasma osmolality, serum sodium and potassium levels, and vital signs, the patient receives desmopressin. A normal response produces a leveling of the urine osmolarity of at least 600 mOsm/kg H\(_2\)O, with less than a 5% increase after desmopressin administration. This would be the case with primary polydipsia where, despite normal urine concentration, it does not reduce polydipsia and thirst. If the patient has an increase in urine osmolarity and desmopressin is given, the diabetes insipidus is considered to be central. However, if there are a submaximal increase in urine osmolarity and a lack of response after desmopressin administration, it is determined that the diabetes insipidus is nephrogenic.

The urine osmolarity of patient 1 (Figure) did not increase as expected. On the basis of our test, his urine osmolarity neither concentrated enough nor concentrated more than 5% after desmopressin administration. According to these findings, he had nephrogenic diabetes insipidus.

Although tenofovir is an NRTI shown to have good antiviral activity against both wild-type and resistant strains of HIV, it has been associated with nephrotoxicity because of damage to proximal tubular cells and the collecting duct cells.\(^4\) Normal excretion occurs through tenofovir entering the proximal tubule from the peritubular capillaries via 1 of the 2 human organic anion transporters.
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(hOATs) (type 1 or type 3), which are localized to the basolateral membrane. Initially, tenofovir was thought to be secreted into the tubular lumen via the multidrug-resistant protein (MRP) type 2. Recent in vitro studies have shown that it is also secreted into the urine via MRP type 4, which is localized to the apical membrane. Thus, tenofovir is a substrate of MRP type 2 and MRP type 4. In addition, genetic polymorphisms of hOAT and MRP have a role in the renal excretory process. There are 2 postulated pathophysiological mechanisms for renal damage. One hypothesis is based on the mechanism of damage that occurs with concomitant use of tenofovir and didanosine. Although clinicians rarely prescribe this antiretroviral therapy combination because of increased risk of drug-related toxicity and virological failure, the fact that all of our patients were receiving such therapy at presentation is difficult to ignore.

The pathophysiological mechanism of renal failure is proposed to be caused by tenofovir and didanosine competing for hOAT1 and hOAT3, thereby inhibiting the excretion of didanosine. This dual process allows higher levels of didanosine in serum and, thus, increases the risk of mitochondrial damage and renal toxicity, especially during concomitant administration of both drugs. Serum didanosine levels have been shown to increase up to 60% when used in combination with tenofovir, supporting this hypothetical mechanism. The other controversial and postulated method of nephrotoxicity is based on the concomitant administration of tenofovir with a protease inhibitor. It had been hypothesized that protease inhibitors—specifically ritonavir—prevent the tubular secretion of tenofovir into the urine, thus increasing the intracellular concentration of tenofovir through their inhibition of MRP type 2. In addition, some investigators have shown that concomitant use of ritonavir and tenofovir, whether or not in combination with lopinavir, increases serum tenofovir concentrations by more than 30%. Overall, the data are controversial because pharmacological studies have shown a low potential for protease inhibitors to interfere with the tubular secretion of tenofovir. Izzedine and colleagues have postulated that concomitant administration of tenofovir with ritonavir is associated with nephrogenic diabetes insipidus. As mentioned herein, nephrogenic diabetes insipidus is characterized by an unresponsiveness of the kidney to ADH. Ritonavir has also been associated with the inhibition of MRP type 1, leading to an increased insensitivity of the kidney to ADH. Patient 1 was not taking ritonavir, which raises the question of whether another pathophysiological mechanism can produce nephrogenic diabetes insipidus unrelated to ritonavir. Our case series is unique in that of these 3 patients in whom nephrogenic diabetes insipidus developed while they were receiving antiretroviral therapy, 2 were receiving a regimen of tenofovir, didanosine, and protease inhibitors, specifically ritonavir, but the other was not exposed to protease inhibitor therapy. This result raises the question of whether the use of didanosine is a potential influence in producing nephrogenic diabetes insipidus.

The use of didanosine has also been associated with Fanconi syndrome and nephrogenic diabetes insipidus in a case report by D’Ythurbide and colleagues. On the basis of their data collection, the cases of tenofovir-associated Fanconi syndrome reported did not involve didanosine use. However, the cases of nephrogenic diabetes insipidus that they reviewed were associated with didanosine use. Concomitant use of tenofovir and didanosine increased didanosine concentrations; after discontinuation of tenofovir therapy, the nephrogenic diabetes insipidus—and proximal tubular dysfunction—also improved. This effect may be the result of the decreasing concentration of didanosine. The case reported by these investigators, who showed that the use of didanosine was associated with Fanconi syndrome and nephrogenic diabetes insipidus, is suggestive of an association with didanosine. To our knowledge, isolated Fanconi syndrome with diabetes insipidus and without didanosine use is limited to one patient from a case series. Despite the controversy, our cases still underscore the importance of frequent monitoring of renal function when tenofovir is used, particularly when the therapy is combined with protease inhibitors or didanosine, or both. On the basis of our experience, there should be frequent monitoring of electrolytes, creatinine, blood urea nitrogen, and phosphorus levels and a urinalysis completed specifically for evaluation of glycosuria and proteinuria when using tenofovir therapy. Any adverse change either in the level of serum creatinine or electrolytes or in the urinalysis results should raise suspicion for early signs of renal damage possibly ascribed to the use of tenofovir. Renal toxicity can usually present after 20 weeks or more of tenofovir therapy, with resolution typically within 10 weeks after the discontinuation of the therapy. This observation is based on anecdotal experience from case reports. Discontinuation of the offending agent is known to be the first step to recovery. Fortunately, as shown in our patients and in other cases reported in the medical literature, renal function recovers after tenofovir is discontinued.

No potential conflict of interest relevant to this article was reported by the authors.
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