## *Perspective*

# Renal Dysfunction and Tenofovir Toxicity in HIV-infected Patients

*Potentially nephrotoxic drugs are only 1 of several causes of renal dysfunction in HIV. Data from the period before the wide use of tenofovir show a variety of prerenal, renal, and obstructive causes of acute renal failure (ARF) in HIV outpatients. Results of clinical trials of tenofovir indicate a rate of ARF of approximately 1%, with observational cohort data indicating a somewhat higher rate. Thus, in evaluating patients with rising serum creatinine levels, including those receiving tenofovir, diagnostic efforts should go beyond discontinuation of potentially offending drugs. This article summarizes a presentation on renal dysfunction in HIV and renal toxicity of antiretroviral drugs made by Lynda A. Szczech, MD, MSCE, at an International AIDS Society–USA Continuing Medical Education course in Washington, DC, in May 2008. The original presentation is available as a Webcast at www.iasusa.org*

As HIV practitioners, we are often caught in the position of determining whether complications arising in our patients stem from the treatments we have used in an effort to help them. An enduring lesson from the Strategies for Management of Antiretroviral Therapy (SMART) trial is that although we have to expect toxicities from HIV medications and know how to manage them, delaying or suspending medication use can have worse consequences. In that study, patients underwent randomization to continuous antiretroviral therapy (viral-suppression group) or a drug-conservation strategy in which treatment was deferred or suspended when CD4+ count was higher than 350 cells/μL and started or resumed when the count fell below 250 cells/μL. Risk of death from any cause or opportunistic infection, risk of major cardiovascular, renal, or hepatic disease, and risks of cardiovascular and renal disease separately were statistically significantly lower in the viral-suppression group than in the drug-conservation group. For fatal or nonfatal renal disease, the hazard ratio in the drug-conservation group was 4.5 ($P$ = .05) (SMART Study Group et al, *N Engl J Med*, 2006).

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## Renal Dysfunction in HIV

Renal dysfunction has numerous causes in our patients. Acute renal failure (ARF) is signalled by a marked acute rise in serum creatinine level, but no specific magnitude of increase defines the condition. In the HIV outpatient population, Franceschini and colleagues (*Kidney Int*, 2005) reported a rate of ARF of 5.9 cases per 100 person-years in 754 patients observed from 2000 to 2002. Rates of ARF in HIV outpatients were reported at 2.9% in 1995 and 6.0% in 2003 in a study of 25,114 patients (Wyatt et al, *AIDS*, 2006).

In the study by Franceschini and colleagues, ARF had prerenal causes (mostly diarrhea and nausea/vomiting or infection) in 38% of cases, renal causes (mostly ischemic or medication-related) in 46%, and obstructive causes in 7% (Table 1) (Franceschini et al, *Kidney Int*, 2005). The study was conducted before the heavy penetration into clinical practice of the nucleotide analogue reverse transcriptase inhibitor (nRTI) tenofovir, the antiretroviral drug most associated with renal toxicity. The data should serve as a reminder that, even in the patient receiving tenofovir, numerous factors can cause renal dysfunction.

When evaluating a patient with a rising serum creatinine level indicative of abnormal renal function, the practitioner should first determine whether the patient is in the "glomerular" group (ie, has a disease affecting the glomeruli) or the "tubular" group (ie, has a lesion affecting the tubules) (Figure 1). The urinalysis is essential in this determination. In broad terms, glomerular dysfunction in HIV patients may be indicative of HIV-related kidney disease or other secondary diseases such as diabetes mellitus, whereas drug toxicities more often manifest as tubular dysfunction. Glomerular involvement is indicated by the finding of protein-

Table **1.** Causes of Acute Renal Failure in HIV Outpatients, 2000 to 2002, Before Widespread Use of Tenofovir

| Prerenal, n = 43, 38% |
| --- |
| Diarrhea, nausea/vomiting: 18 |
| Heart failure: 2 |
| Hepatorenal: 9 |
| Pancreatitis: 2 |
| Adrenal insufficiency: 1 |
| Infection: 10 |
| Erythroderma: 1 |
| **Renal, n = 48, 46%** |
| Acute tubular necrosis<br>  Ischemic: 22<br>  Medications: 17<br>  Contrast: 2 |
| Allergic interstitial nephritis: 5 |
| Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome: 2 |
| **Obstructive, n = 9, 7%** |
| Kidney stones: 2 |
| Crystalluria: 6 |
| Gross hematuria: 1 |

Adapted from Franceschini et al, *Kidney Int*, 2005.

uria alone or combined with hematuria; the presence of hematuria alone probably signifies a problem outside of the kidney parenchyma such as in the ureter, bladder, or prostate.

The role of the tubule is to separate substances for resorption from those for excretion, and tubular dysfunction is suggested by abnormalities in dilution or acidification of urine. Isosthenuria (indicated by urine specific gravity of 1.010) shows that the renal tubules are neither diluting or concentrating the urine. Although this is not necessarily a sign of pathology, it may indicate tubular damage. The presence of casts in urine may also be indicative of tubular dysfunction. Urine is often bland (ie, contains no protein or blood) if there is tubular dysfunction but the glomeruli are intact.

Among tubular disorders, acute tubular necrosis (ATN) consists of damage to tubular cells and results in accumulation of an aggregate of Tamm-Horsfall protein and degenerated cells that form into casts. Direct tubular cell toxicity can be caused by such agents as aminoglycosides, amphotericin B, radiocontrast, pentamidine, heroin or cocaine, nonsteroidal anti-inflammatory drugs, adefovir, and tenofovir. Volume depletion can also result in ATN when reduced perfusion limits blood flow to tubular cells.

Allergic interstitial nephritis (AIN) is a more insidious process in which allergic reaction within the interstitium results in infiltration of inflammatory and plasma cells that inhibit tubule function and damage the interstitium. Drugs that can cause AIN include beta-lactam antibiotics, quinolones, sulfonamides, rifampin, phenytoin, and atazanavir. Casts in the urine are less common in AIN than in ATN.

In Fanconi syndrome, tubular resorption of glucose, phosphate, amino acids, bicarbonate, sodium, or any combination of these is blocked, usually only partially, and urinary wasting occurs. These resorptive abnormalities can manifest as glycosuria in a patient with a normal serum glucose level, low serum phosphorus level (and a compensatory increase in serum parathyroid hormone level), proximal renal
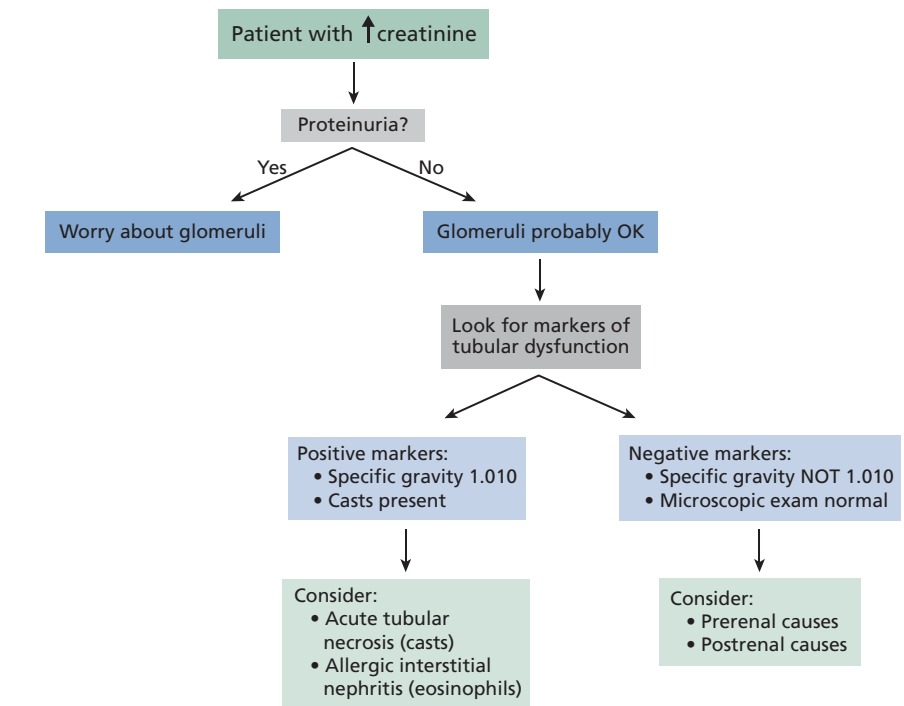


Figure **1.** A simple flow diagram for evaluating HIV patients with increased serum creatinine levels.

tubular acidosis, or volume depletion. Renal loss of phosphate is indicated by increased levels of urine phosphate ($> 5$-$10$ mg/dL or $> 100$ mg/day) and a value for the fractional excretion of phosphorus that is greater than 5% (as calculated using the following formula: [urine phosphate level $\times$ serum creatinine level] $\div$ [serum phosphate level $\times$ urine creatinine level]). Nonrenal phosphate loss (eg, via gastrointestinal loss) or poor oral intake is indicated by a decreased urine phosphate level ($< 5$-$10$ mg/dL or $< 100$ mg/day) and a value for the fractional excretion of phosphorus that is less than 5%.

## Renal Effects of Antiretroviral Drugs

Apart from a number of case reports of interstitial nephritis associated with atazanavir, concern over antiretroviral drug–associated renal toxicity largely has been focused on tenofovir. The literature on renal toxicity of tenofovir is nonstandardized, but studies assessing prior clinical trials and observational cohorts are all limited by lack of diagnostic specificity for the cause of the renal event, thereby producing confu-

sion about the true frequency of this complication.

In the selected populations enrolled in these clinical trials, which include rigorous monitoring of renal function, tenofovir appears to be associated with a low risk of adverse renal effects. The recently reported Head-to-Head Epzicom and Truvada (HEAT) trial compared 343 subjects treated with abacavir/lamivudine with 345 subjects given tenofovir/emtricitabine, both in combination with lopinavir/ritonavir for 48 weeks in treatment-naive patients (Smith et al, CROI, 2008). Reduced glomerular filtration rate (GFR) was noted in 5% of each treatment group, and ARF occurred in less than 1% of patients in the tenofovir/emtricitabine group and none in the abacavir/lamivudine group. Assessment of renal function at 48 weeks showed median changes in the abacavir/lamivudine group similar to those in the tenofovir/emtricitabine group in creatinine clearance, using the Cockcroft-Gault formula ($+9$ vs $+6$ mL/min, respectively), in estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula ($+7$ vs $0$ mL/min/1.73 m$^2$, respectively), in the protein:creatinine ratio ($-0.01$ vs

0, respectively), in serum phosphate level (− 0.3 vs − 0.4 mg/dL, respectively), and in urine glucose concentration (0 vs 0 mg/dL, respectively).

In the ALERT trial, 106 treatment-naive patients received a tenofovir/emtricitabine backbone plus either fosamprenavir/ritonavir or atazanavir/ritonavir (Smith et al, IAC, 2007). Mean changes in GFR adjusted for body weight were approximately + 4 and − 4 mL/min/1.73 m$^2$ at 48 weeks in the fosamprenavir/ritonavir and atazanavir/ritonavir groups, respectively.

The single-arm Boosted Atazanavir and Truvada Given Once Daily (BATON) trial examined atazanavir plus tenofovir/emtricitabine in 102 treatment-naive patients (Gilead Sciences, Foster City, CA, data on file). Over 48 weeks, creatinine clearance decreased from 109 mL/min to 104 mL/min using the Cockcroft-Gault equation, and the GFR using the MDRD formula decreased from 93 mL/min/1.73 m$^2$ to 80 mL/min/1.73 m$^2$. One patient discontinued tenofovir/emtricitabine early because of a grade 1 increase in serum creatinine level; 2 additional patients had confirmed graded increases (grade 1 and grade 2).

It is unclear how to interpret the group change in MDRD measurement with regard to individual patient risk. Do we expect every patient to exhibit on average a 13 mL/min/1.73 m$^2$ decrease in GFR, or will a small number of subjects experience more substantial changes associated with ARF? In the Gilead 934 study, 517 treatment-naive patients received efavirenz plus tenofovir/emtricitabine or zidovudine/lamivudine/efavirenz for 144 weeks, after which all patients received efavirenz/tenofovir/emtricitabine for an additional 96 weeks. At 144 weeks, there was no statistically significant difference in change from pretreatment levels in median creatinine clearance using the Cockcroft-Gault equation in either treatment group (118 vs 115 mL/min for zidovudine/lamivudine and tenofovir/emtricitabine, respectively, from a pretreatment value of 121 mL/min for both). However, the change from pretreatment using the MDRD equation was statistically significantly

greater in the tenofovir/emtricitabine group (from median 110 to 98 mL/min/1.73 m$^2$) than in the zidovudine/lamivudine group (from median 105 to 106 mL/min/1.73 m$^2$) ($P$ < .001).

The finding of no difference in change between the tenofovir comparator groups using the Cockcroft-Gault equation but some difference using the MDRD equation is similar to observations from the HEAT trial. While a discussion of the limitations of each formula is beyond the scope of this presentation, it should be noted that both use demographic and clinical variables to approximate muscle mass and "normalize creatinine." The differences between formulae are based on the relative emphasis of age and sex as well as the presence of weight in the Cockcroft-Gault formula and race in the MDRD formula. The consideration of how a differential change in weight could have masked a "real" change in renal function using the Cockcroft-Gault formula or, conversely, how the addition of lean body mass could result in the "appearance" of a change in renal function using the MDRD formula should be further explored.

This trend did not continue in longer term observation, however. In the continuation group of the trial (study 903E), treatment with tenofovir for up to 6 years was associated with at least stability in renal function, with creatinine clearance level increasing from 116 mL/min to 128 mL/min ($P$ = .015) using the Cockcroft-Gault equation, and with the estimated GFR increasing from 112 mL/min/1.73 m$^2$ to 117 mL/min/1.73 m$^2$ ($P$ = .058) using the MDRD equation (Gilead Sciences, data on file).

The clinical trial data suggest that risk of tenofovir renal toxicity is low (approximately 1%) in selected populations with good dosing practices and vigilance in patient monitoring. However, some observational cohort studies suggest a higher risk—not surprising given that patient populations are more heterogeneous and treatment is more complex in real life. Rates of tenofovir nephrotoxicity in retrospective cohort studies have been reported in general at approximately 2% (1.90% [Karras et al, *Clin Infect Dis*, 2003],

1.60% [Padilla et al, *AIDS Patient Care STDS*, 2005], 0.80% [Jones, *JAIDS*, 2004], 0.78% [Franceschini, *Kidney Int*, 2005], and 0.00% [Gallant et al, *Clin Infect Dis*, 2005]).

Variation in incidence in these reports may be attributable to surveillance and recognition biases, lack of a standard definition of toxicity, and reporting of mean versus median renal function values. Whether the frequency of tenofovir-related ARF is approximately 1%, as suggested by clinical trials, or approximately 2%, as might be surmised from cohort studies, recall the background rate of ARF in the HIV population of approximately 6%, as observed in the study by Franceschini and colleagues conducted before the wide use of tenofovir. It is thus potentially dangerous to assume that all cases of impaired renal function in a patient receiving tenofovir are caused only by tenofovir and to respond to such a finding by simply stopping the drug without a thorough search for other causes. Failure to consider other causes may result in a missed opportunity for an early diagnosis of another condition that could be the real culprit and that may continue unchecked.

That said, it is still instructive to examine observational cohort data closely to derive an idea of risk in the clinical setting. Johns Hopkins cohort data showed significant reductions in creatinine clearance at 180 days, 270 days, and 360 days over a 360-day follow-up in 344 patients receiving tenofovir compared with 314 patients who received nRTIs other than tenofovir (Gallant et al, *Clin Infect Dis*, 2005). Pretreatment values and changes in renal function are shown in Table 2.

A study in the HIV Outpatient Study (HOPS) cohort examined the potential effects of concomitant protease inhibitor (PI) and tenofovir treatment. Over 12 months, median changes in creatinine clearance were − 2.8 mL/min versus − 5.1 mL/min, respectively, in patients without PI exposure (n = 210) versus those receiving atazanavir/ritonavir or lopinavir/ritonavir (n = 99) in addition to tenofovir ($P$ = .51); median changes in GFR were − 5 mL/min/1.73 m$^2$ versus − 5 mL/

Table **2.** Changes in Renal Function in Patients Receiving Tenofovir Versus Nucleoside Analogue Reverse Transcriptase Inhibitors (nRTIs) in the Johns Hopkins Cohort

| | Tenofovir Group (n = 344) | nRTI Group (n = 314) | *P* Value |
|---|---|---|---|
| Serum creatinine at pretreatment, mg/dL | 0.8[a] | 0.8 | .56 |
| Creatine clearance at pretreatment, mL/min | 117 | 118 | .69 |
| Treatment period, days | 303 | 336 | .19 |
| Maximum serum creatinine, mg/dL | 1.0 | 0.9 | .17 |
| Absolute change in serum creatinine, mg/dL | +0.15 | +0.10 | .17 |
| Calculated minimum creatine clearance, mL/min | 98 | 102 | .43 |
| Absolute change in creatine clearance, mL/min | −13.3 | −7.5 | .005 |
| Percent change in creatine clearance | −10 | −6 | .007 |
| Patients with decline in creatine clearance, no. (%) | | | .14 |
| >50% | 15 (4.4) | 6 (1.9) | |
| 25%-50% | 46 (13.4) | 34 (10.8) | |
| 1%-50% | 158 (45.9) | 141 (44.9) | |
| No decline | 125 (36.3) | 133 (42.3) | |

[a]Data are median unless otherwise indicated.
Adapted from Gallant et al, *Clin Infect Dis*, 2005.

min/1.73 m$^2$ in patients without (n = 208) or with (n = 97) PI exposure (*P* = .55) (Buchacz et al, *JAIDS*, 2006). However, a recent study indicated a statistically significant reduction (approximately 13 mL/min) in creatinine clearance at 48 weeks in 51 patients receiving tenofovir and lopinavir/ritonavir compared with 66 patients not receiving tenofovir and 29 receiving tenofovir plus nonnucleoside reverse transcriptase inhibitors (NNRTIs), with the change in the latter 2 groups (an approximate 5 mL/min reduction) being similar (Goicoechea et al, *J Infect Dis*, 2008)

## Summary

The risk of toxicities from drugs used in HIV clearly exists, but the risk of kidney dysfunction is even greater when HIV goes untreated too long. Various causes of ARF in HIV patients can be major clinical problems. Stopping a drug with recognized renal adverse effects is the correct course of action for a patient with ARF, but we should not lose sight of the fact that other causes may lead to loss of function and that drug discontinuation alone can leave us with a clear but unsupported opinion on causality of the ARF in our increasingly complex patients.

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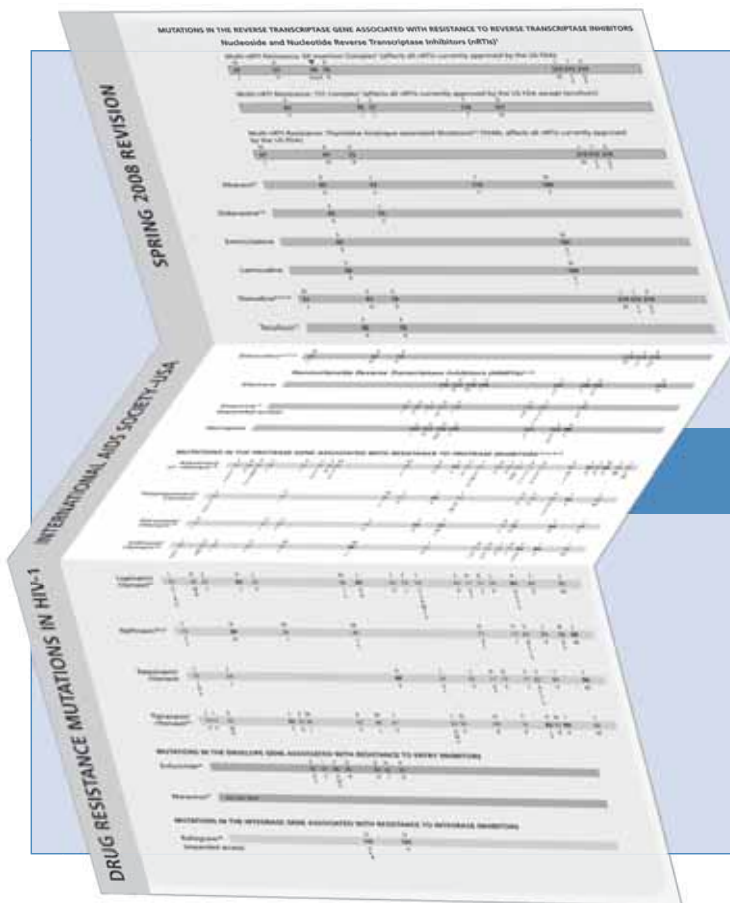
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