Acute kidney injury (AKI) and chronic kidney disease (CKD) are more common in the HIV-infected population than in the general population. AKI is associated with an increased risk of heart failure, cardiovascular disease, end-stage renal disease (ESRD), and mortality. Tenofovir is associated with severe AKI in a small percentage of patients and with subclinical abnormalities in many more. HIV-associated nephropathy is now a relatively rare form of CKD, because of the widespread use of potent antiretroviral therapy. The CKD spectrum in HIV-infected patients has become more frequently characterized by comorbid CKD, with an increased frequency of CKD related to diabetes or hypertension being observed. Kidney transplantation is a therapeutic option for HIV-infected patients with ESRD if their HIV infection is controlled, although rates of acute graft rejection and drug-drug interactions are high. This article summarizes a presentation by Christina M. Wyatt, MD, at the IAS–USA continuing education program held in Washington, DC, in June 2013.

Keywords: acute kidney injury, chronic kidney disease, end-stage renal disease, HIV, nephrotoxicity, renal, tenofovir, toxicity, transplantation

Acute Kidney Injury

Acute kidney injury (AKI) is more common in HIV-infected patients than in the general population and is associated with poorer health outcomes in those with HIV infection, including increased rates of heart failure, cardiovascular disease, end-stage renal disease (ESRD), and mortality. Even stage I AKI is associated with an increased risk of ESRD and mortality (Figure 1).1,2

In a 2005 study of more than 700 HIV-infected patients, approximately 10% of patients experienced at least 1 episode of AKI over the 2-year follow-up period. The investigators determined that 52% of cases were caused by systemic infections, 76% of which were AIDS-defining infections.3 Thirty-two percent of cases were caused by drug toxicity, with most cases attributed to the use of β-lactam or aminoglycoside antibiotics and some to the antiretroviral drugs indinavir and tenofovir, radiocontrast agents, nonsteroidal antiinflammatory drugs, or lithium. Another 10% of cases were attributed to liver failure, with 90% of these occurring in patients with hepatitis C virus (HCV) coinfection.

Case Study

A 56-year-old, HIV/HCV-coinfected, African American woman with well-compensated cirrhosis presented to her primary care practitioner in the HIV clinic with a complaint of vomiting that persisted for 2 weeks. Her most recent CD4+ cell count was approximately 300/µL and her nadir CD4+ cell count was less than 100/µL. Her antiretroviral regimen consisted of tenofovir, emtricitabine, and ritonavir-boosted (r) lopinavir. She had also been taking ibuprofen for malaise.

Her laboratory results were remarkable for a serum creatinine level of 21 mg/dL (the most recent serum creatinine was 1.4 mg/dL), a blood urea nitrogen level of 78 mg/dL, a serum potassium level of 3.9 mEq/L, and a serum bicarbonate level of 15.2 mEq/L. Urinalysis showed protein, ketones, and glucose (serum glucose was normal), and a normal bowel gas pattern was found on plain film radiographic examination. Additional laboratory evaluation showed a serum phosphorus level of 5.2 mg/dL and a urine sodium level of 60 mEq/L.

The most likely cause of AKI in this case is tenofovir toxicity. Although the classic presentation of tenofovir toxicity is proximal tubulopathy, the classic electrolyte deficiencies (hypophosphatemia, hypokalemia, hypouricemia) may not be present in patients who present with severely reduced glomerular filtration rate; in this case, the absence of hyperkalemia in the context of renal failure and acidosis was notable. The finding of urine glucose in the setting of a normal

Dr Wyatt is Associate Professor of Medicine at the Icahn School of Medicine at Mount Sinai in New York, New York.
Biopsy is usually not necessary to diagnose tenofovir kidney toxicity. The presentation is generally that of proximal tubulopathy with wasting of phosphorus, glucose, amino acids, and bicarbonate, which are reabsorbed by the proximal tubule under normal circumstances. In most instances, toxicity resolves when tenofovir is discontinued. Biopsy may be warranted when there is a compelling reason not to discontinue tenofovir (eg, in patients with hepatitis B virus coinfection who are not candidates for entecavir or those with an antiretroviral resistance profile that limits therapeutic options) or if the clinical picture does not clearly suggest tenofovir toxicity. In cases of tenofovir toxicity, biopsy shows damage to the proximal tubule, whereas the glomerulus typically remains unaffected (Figure 2). The advanced fibrosis evident in the figure indicates chronic toxicity. If tenofovir toxicity is identified early, it may be completely reversible, but irreversible damage is likely with chronic toxicity.

More remains to be learned about risk factors for tenofovir toxicity, but unrecognized low glomerular filtration rate (GFR) is an established risk factor, as is concomitant administration of another nephrotoxic drug. Some data suggest a genetic predisposition to tenofovir toxicity, although most of the early studies in this area focused on membrane transport proteins that are not actively involved in tenofovir transport. The transport of tenofovir from the basolateral (blood) side of tubule cells is mediated primarily by organic anion transporter (OAT) 1 and to a lesser extent by OAT3 (Figure 3, top).4,9 The exit of tenofovir to the apical (urine) side of tubule cells is mediated by multidrug resistance protein (MRP) 4. Most early genetic studies of tenofovir toxicity focused on MRP2, based on observation of an association between ritonavir-boosted protease inhibitor (PI) use and tenofovir toxicity, and the known effect of ritonavir in interfering with MRP2-mediated efflux of other drugs. However, more recent studies suggest that the association of boosted PI use with tenofovir toxicity reflects the effect of some boosted PIs in increasing biologic availability and trough blood levels of tenofovir.10

Data from the EuroSIDA cohort showed that use versus nonuse of tenofovir, indinavir, atazanavir, or lopinavir/r was associated with a statistically significantly increased risk of developing chronic kidney disease (CKD), manifested as a confirmed creatinine clearance of less than 60 mL/min per 1.73 m2.11 There is evidence indicating that atazanavir, like indinavir but to a lesser degree, can precipitate into crystals, resulting in an inflammatory reaction and interstitial nephritis, a mechanism supported by

Figure 2. Kidney biopsy showing the effects of tenofovir renal toxicity. Courtesy of Glen S. Markowitz, MD, and Vivette D. D’Agati, MD.

Figure 3. Tubular transport of tenofovir (top) and effect of antiretroviral therapy on creatinine secretion (bottom). MRP indicates multidrug resistance protein; Na-K, sodium-potassium; OAT, organic anion transporter; OCT, organic cation transporter. Adapted from Ray et al.4 aInhibited by ritonavir. bInhibited by dolutegravir. cInhibited by trimethoprim, cobicistat, or rilpivirine.

serum glucose (euglycemic glycosuria) is another indicator of proximal tubular injury. Although the history could suggest hepatorenal syndrome or prerenal AKI, the patient has well-compensated cirrhosis and the high urine sodium level is more consistent with intrinsic kidney damage.

Tenofovir Toxicity

Although tenofovir was not associated with a statistically significant increase in kidney toxicity in premarketing clinical trials, graded elevations in serum creatinine were observed in 2.2% of patients receiving tenofovir through the manufacturer’s expanded access program.4 Subclinical abnormalities suggesting proximal tubular dysfunction have been observed in 25% to 80% of patients.5-7 A 2010 meta-analysis of 5 randomized controlled trials of tenofovir and 8 cohort studies of antiretroviral therapy–naive and –experienced patients showed small but statistically significantly greater reductions in calculated creatinine clearance among tenofovir recipients in the randomized trials, the cohort studies, and all studies combined. Overall, the mean difference between tenofovir recipients and nonrecipients was -3.9 mL/min, with larger differences observed in the cohort studies. A statistically significant decline in tenofovir recipients was observed in only 1 of the controlled trials when analyzed separately.8
the relatively high levels of atazanavir found in the urine. A similar mechanism may account for the apparent increase in CKD associated with the use of lopinavir/ritonavir. Assessment of the relationship between antiretroviral therapy exposure and CKD in the D:A:D (Data Collection on Adverse Events of Antiretroviral Therapy) cohort showed that on multivariate analysis, atazanavir (incidence rate ratio [IRR], 1.18), lopinavir/ritonavir (IRR, 1.11), and atazanavir/ritonavir (IRR, 1.19)—but not unboosted atazanavir, other ritonavir-boosted PIs, or abacavir—were associated with a statistically significantly increased risk of having an estimated GFR (eGFR) less than or equal to 70 mL/min per 1.73 m². Only lopinavir/ritonavir (IRR 1.22) was associated with a statistically significantly increased risk of having an eGFR less than or equal to 60 mL/min per 1.73 m². The investigators noted a high rate of tenofovir discontinuation at eGFR less than 70 and hypothesized that this may have prevented further declines in kidney function.

Tenofovir was recently approved by the US Food and Drug Administration (FDA) for use in combination with emtricitabine for HIV preexposure prophylaxis (PrEP). Although randomized controlled trials of tenofovir in this setting have not shown overt bone or renal toxicity, it should be remembered that trials of tenofovir in HIV-infected patients also did not show overt bone or renal toxicity, and that most PrEP studies have shown low medication adherence rates. In the iPrEx (Chemo prophylaxis for HIV Prevention in Men) study, a greater decline in creatinine clearance was observed in patients receiving tenofovir in combination with emtricitabine, indicating that renal toxicity may also occur in HIV-uninfected persons receiving tenofovir for PrEP.

Another recent development is the FDA approval of a fixed-dose combination of tenofovir, emtricitabine, elvitegravir, and cobicistat. Cobicistat has been associated with rapid and reversible declines in eGFR with no decrease in measured GFR. This reflects an increase in serum creatinine resulting from decreased tubular creatinine secretion via the multidrug and toxin extrusion protein 1 (MATE1) transporter (Figure 3, bottom). The effect of cobicistat on the MATE1 transporter is similar to but of lesser magnitude than the inhibitory effect of the antibiotic trimethoprim. Studies in vitro have shown that the MATE1 transporter is also inhibited by rifampin, another antiretroviral drug used in fixed-dose combination with tenofovir. Dolutegravir may cause an increase in serum creatinine levels similar to that seen with cobicistat use by inhibiting the organic cation transporter 2 (OCT2), which transports creatinine into tubular cells. The average increase in serum creatinine level seen with cobicistat is approximately 0.1 mg/dL to 0.15 mg/dL, although some patients exhibit more marked increases. Increases in serum creatinine levels generally occur very rapidly after initiation of therapy with cobicistat and should be detectable within approximately 2 weeks.

Tenofovir alafenamide fumarate (formerly GS-T430), which is in phase III studies, produces lower plasma levels of tenofovir. Phase II studies of this drug showed reduced adverse effects in bone and kidneys, and pharmacokinetic evaluation indicates that no dose reduction is required in patients with GFRs as low as 15 mL/min per 1.73 m² to 30 mL/min per 1.73 m².

**Chronic Kidney Disease**

**HIV-Associated Nephropathy**

HIV-associated nephropathy (HIVAN)—the classic kidney disease of HIV infection—is decreasing in incidence in the era of aggressive antiretroviral therapy. HIVAN is associated with advanced HIV disease and almost exclusively affects patients of African American or West African descent, as a result of a genetic predisposition that has been well described in the last several years. IAS–USA, Infectious Diseases Society of America, and US Department of Health and Human Services guidelines all indicate that diagnosis of HIVAN is an indication for the initiation of antiretroviral therapy regardless of CD4+ cell count. In practice, the guideline to start treatment on the basis of HIVAN rarely needs to be invoked, because most patients have low CD4+ cell counts at the time of presentation with HIVAN and antiretroviral therapy is indicated regardless of CD4+ cell count.

**The Changing Spectrum of CKD**

The spectrum of CKD in HIV now reflects an increased frequency of comorbid kidney disease, including increased frequency of diabetes and hypertension, which are the leading causes of ESRD in the general population. Treatment of comorbid disease in HIV-infected patients involves the same measures used in the general population, including tight control of blood pressure and glycemia.

CKD is associated with increased cardiovascular risk, but there are limited data on the effect of risk modification in reducing the incidence of cardiovascular disease in this setting. Drug choice and dosing should be reviewed in patients with comorbid CKD. Kidney biopsy is underused for diagnosis of CKD in the HIV-infected population, particularly in patients who are candidates for kidney transplant. It is helpful to have biopsy information in advance and available data indicate that there is no increase in biopsy procedural risk in HIV-infected patients. Referral to a nephrology specialist for ESRD treatment planning should be made by the time a patient reaches CKD stage 4 (eGFR < 30 mL/min per 1.73 m²), if not sooner.

In ESRD treatment, survival outcomes with peritoneal dialysis and hemodialysis are basically equivalent in the HIV-infected population, although infectious complications differ with the 2 modalities. Kidney transplantation is an additional treatment option for ESRD. The best data supporting transplantation in the HIV-infected population come from a large prospective observational study of 150 HIV-infected patients, reported by Stock and colleagues in 2010. To take part in the study, patients had to have undetectable HIV RNA levels and CD4+ cell counts greater than 200/μL and be on a stable potent antiretroviral regimen. Acceptable graft and patient survival rates were achieved and were similar to rates observed in transplant recipients older than 65 years of age in the HIV-uninfected population. There was no apparent increase
in opportunistic infections among study patients; 5 AIDS-defining illnesses, 7 non-AIDS-defining cancers, and 2 cases of biopsy-proven HIVAN were reported; except for the HIVAN cases, these were all conditions known to occur in HIV-infected transplant recipients. A high rate of acute graft rejection and marked drug-drug interactions were observed.

Pls can dramatically increase levels of calcineurin inhibitors, such that administration of calcineurin inhibitors may need to be reduced from twice daily to as infrequently as once weekly during concurrent PI use. Although high calcineurin inhibitor levels can be maintained in this manner, there is suspicion that a reduced consistency in exposure may be contributing to the increased rate of acute graft rejection seen in HIV-infected patients. Nonnucleoside reverse transcriptase inhibitors have a more moderate effect in reducing levels of calcineurin inhibitors. Switching patients to PI-sparing regimens prior to kidney transplantation is required by some transplant centers; switching to a PI-sparing regimen after transplantation is also an option, and there are pros and cons associated with both approaches. Limited data are available on the use of tenofovir in HIV-infected transplant recipients, although it appears to be well tolerated.

Conclusion
AKI and CKD are more common among HIV-infected patients than in the general population. It may be difficult to distinguish antiretroviral nephrotoxicity from other causes of AKI or CKD, and there is an increasing prevalence of comorbid CKD in the HIV-infected population. Patients with controlled HIV infection may be candidates for kidney transplantation, although the potential for severe drug-drug interactions should be recognized.

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Additional Suggested Reading


References