Kidney Disease in Patients with HIV Infection and AIDS

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As patients infected with human immunodeficiency virus (HIV) live longer while receiving antiretroviral therapy, kidney diseases have emerged as significant causes of morbidity and mortality. Black race, older age, hypertension, diabetes, low CD4+ cell count, and high viral load remain important risk factors for kidney disease in this population. Chronic kidney disease should be diagnosed in its early stages through routine screening and careful attention to changes in glomerular filtration rate or creatinine clearance. Hypertension and diabetes must be aggressively treated. Antiretroviral regimens themselves have been implicated in acute or chronic kidney disease. The risk of kidney disease associated with the widely used agent tenofovir continues to be studied, although its incidence in reported clinical trials and observational studies remains quite low. Future studies about the relationship between black race and kidney disease, as well as strategies for early detection and intervention of kidney disease, hold promise for meaningful reductions in morbidity and mortality associated with kidney disease.

HISTORICAL PERSPECTIVE

The first reports of AIDS-related renal failure, published in the mid-1980s, described cases of what we now recognize as HIV-associated nephropathy (HIVAN) [1]. Before effective antiviral therapy became available, HIVAN was so frequent and its clinical features were so dramatic—heavy proteinuria and rapid progression to end-stage renal disease (ESRD) in immunosuppressed black persons—that HIVAN became almost synonymous with HIV-associated chronic kidney disease (CKD). As HIV spread through the black community, the ESRD incidence increased substantially, and by the early 1990s, HIVAN became the third leading cause of ESRD in black persons aged 20–64 years [2].

Since that time, the incidence and spectrum of kidney diseases in HIV-infected patients have been altered by the widespread use of HAART. The clinical course of kidney disease is more indolent, the risk of ESRD has been reduced by 40%–60%, the 1-year survival rate while undergoing dialysis has increased from 25% to 75%, and kidney transplantation is a viable option [3–6]. Despite these improvements, risk factors for kidney disease are highly prevalent among HIV-infected patients, and kidney disease remains a significant cause of morbidity and mortality, even among those patients receiving HAART.

EPIDEMIOLOGY AND RISK FACTORS FOR CKD IN HIV-INFECTED PATIENTS

CKD is defined as kidney damage or reduced kidney function that persists for >3 months [7]. A useful indicator of kidney damage is elevated urinary protein excretion, measured qualitatively with use of a urine dipstick or measured quantitatively with use of a spot urine protein-to-creatinine ratio (or 24-h urine collection). Kidney function can be reliably estimated from the serum creatinine by calculating the creatinine clearance or glomerular filtration rate (GFR) through use of the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) equations, respectively. A GFR <60 mL/min meets criteria for CKD, a cutoff supported by epidemiologic data linking lower GFR to an increased frequency of hospitalization, cardiovascular events, or death. Neither the Cockcroft-Gault nor the MDRD equations has been specifically validated in the HIV-infected population. The MDRD equation was derived from patients with low GFR and therefore can yield variable results in persons with normal renal function [8]. Nonetheless, these estimates remain the most highly validated formulas avail-
persons with HIV infection are more likely to have insulin resistance at least 2-fold [17, 18]. In a comparison between blacks and whites for every 100 cases of CKD in black persons, whereas only 1 new ESRD case develops for every 100 cases of CKD in whites [16]. The burden of kidney disease in black persons with HIV infection, compared with their HIV-infected white counterparts [15]. Five new cases of ESRD develop for every 100 cases of CKD in blacks, whereas only 1 new ESRD case develops for every 100 cases of CKD in whites [16]. The burden of kidney disease in black persons with HIV infection, compared with their HIV-infected white counterparts, is similarly disproportionate. Among persons with HIV infection who receive dialysis, 91% are black [3]. Black race decreases the risk of microalbuminuria and proteinuria by at least 2-fold [17, 18]. In a comparison between blacks and whites in an analysis of >2 million patients who received care through the Veterans Administration system, the multivariate hazard ratio for ESRD in HIV-infected persons was 4.56 (95% CI, 3.44–6.05) [19]. The natural history of CKD is also considerably more aggressive in HIV-infected blacks than in whites. Among 4259 patients observed in the Johns Hopkins HIV Clinical Cohort from 1990 through 2004, the risk for incident CKD was 2-fold higher among blacks (hazard ratio 1.9; 95% CI, 1.2–2.8). After CKD diagnosis, however, the decrease in GFR was 6-fold more rapid among blacks, which dramatically increased the likelihood of progression to ESRD (hazard ratio, 17.7; 95% CI, 2.5–127) [20].

The aging of an HIV-infected population is another important pathway by which the incidence of CKD can be expected to continue to increase. GFR normally decreases with age. The prevalence of CKD in the elderly population now approaches 50% [21]. Other risk factors for CKD in HIV-infected patients are high viral load, low CD4+ lymphocyte count, and hepatitis C virus coinfection [17]. The importance of recognizing CKD is underscored by the strong correlation between CKD and both morbidity and mortality. In the HIV Epidemiology Research Study, proteinuria or an elevated serum creatinine level was associated with an increased risk of hospitalization and mortality [22, 23]. In the Women's Interagency HIV Study, elevated creatinine level and proteinuria were similarly predictive of an increased risk of an AIDS-defining illness and mortality [24].

**Acute renal failure (ARF) in HIV-infected persons.** ARF is highly prevalent among persons with HIV infection and, like CKD, is linked to morbidity and mortality. Major risk factors are the same as in the general population, including older age, preexisting CKD, serious systemic illness or infection, and exposure to nephrotoxic agents [25, 26]. Liver disease and low CD4+ cell count also increase the risk of ARF among HIV-infected persons. Table 1 lists antivirals and antibiotics with nephrotoxic potential that are commonly used in treatment of HIV-infected patients.
Ten percent of patients in a large ambulatory clinic experienced at least 1 episode of ARF over a 2-year period [25]. More than one-half of these episodes were attributed to underlying infections, 76% of which were AIDS-defining illnesses, and almost three-quarters of them necessitated hospitalization. Drug-related complications accounted for nearly one-third of cases—the conventional nephrotoxin amphotericin was most common—and liver disease accounted for 10% of cases. In an analysis of administrative data from >2 million hospital discharges in New York State, HIV infection was associated with a 2.8-fold increase in documented ARF cases [26]. In-hospital mortality was increased nearly 6-fold among HIV-infected patients with documented ARF.

**IMPACT OF ANTIRETROVIRAL THERAPY (ART) ON RENAL FUNCTION**

Proper selection and dose-adjustment of antiretrovirals and other commonly used drugs for patients with kidney disease are important components of care for patients with HIV infection. Tables 2 and 3 summarize the nephrotoxic potential of antiretroviral agents and their recommended dose adjustments for those with kidney disease. Isolated case reports of nephrotoxicity have been reported with almost all agents, but renal disease has been associated with indinavir and tenofovir more often than with other drugs [27, 28].

Indinavir causes nephrolithiasis and chronic interstitial nephritis in as many as 12% of patients who receive it. The mainstay of prevention of this condition is adequate hydration, with intake of at least 1.5 L of noncaffeinated fluid. One report described 4 cases of renal colic and nephrolithiasis in patients who received lopinavir-ritonavir treatment, but a causal effect was not established [29]. Three cases of kidney stones containing atazanavir have been reported, and a review of the US Food and Drug Administration adverse event reporting system detected 12 additional confirmed cases [30–33]. Most cases required hospitalization for pain relief and stent insertion, percutaneous nephrostomy, lithotripsy, or endoscopic surgical extraction. Predisposing factors are unknown, and the drug was discontinued in most but not all cases.

The association of tenofovir with kidney disease has been an area of interest since the drug underwent preclinical testing, because of its structural similarity to adefovir and cidofovir. These acyclic nucleotide analogues are excreted by renal tubule cell uptake and secretion [34]. Cidofovir at therapeutic doses can cause ARF, and a high incidence of ARF was noted when adefovir was tested for treatment of HIV-1 infection at dosages of 120 mg per day, which is 10-fold higher than the dosage for treating hepatitis B virus infection. Both agents induce proximal renal tubule cell damage, clinically characterized by phosphaturia, a modest amount of proteinuria (“tubule” proteinuria), and increases in serum creatinine [35, 36]. Consequently, considerable attention has been paid to the incidence of ARF or long-term reductions in GFR that are induced by tenofovir, with use of data from phase II, III, and IV clinical trials; expanded access programs before drug approval; and observational cohort studies. Case reports of tenofovir-induced ARF do exist, sometimes associated with proteinuria, hypohosphatemia, euglycemic glycosuria, hypouricemia, hypokalemia, or metabolic acidosis. This is known as Fanconi syndrome when most or all components are present.

In fact, tenofovir-associated renal dysfunction is a rare event in prospective clinical trials, particularly among ART-naive patients. No significant change in GFR was demonstrated in a comparison of tenofovir versus stavudine in combination with lamivudine-efavirenz [37] or in a comparison of tenofovir-emtricitabine versus fixed-dose zidovudine-lamivudine with

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported nephrotoxicity</th>
<th>Risk factor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Acute renal failure, interstitial nephritis (rare)</td>
<td>…</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Case reports of nephrolithiasis, interstitial nephritis, reversible renal failure</td>
<td>Not established</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Tubular dysfunction (rare)</td>
<td>…</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Single report of hypersensitivity reaction</td>
<td>…</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Single report of glomerulonephritis</td>
<td>…</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute renal failure</td>
<td>Concomitant treatment with low-dose ritonavir; for nephrolithiasis, urine pH &gt;6, low lean body mass, treatment with trimethoprim-sulfamethoxazole or acyclovir, chronic infection with hepatitis B or hepatitis C virus, warm environmental temperature, high indinavir concentration</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tubular dysfunction (rare)</td>
<td>…</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Reversible renal failure, but nephrotoxicity not definitely established</td>
<td>Concomitant treatment with nephrotoxic drugs, underlying renal pathology</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Tubular dysfunction (rare)</td>
<td>…</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Tubular toxicity, Fanconi syndrome (rare), decreased glomerular filtration rate</td>
<td>Low body weight, impaired baseline renal function, concomitant treatment with potentially nephrotoxic drugs</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>Daily dosage</td>
<td>Dosing in the case of renal insufficiency</td>
</tr>
<tr>
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<tr>
<td><strong>Nucleoside reverse-transcriptase inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 mg PO QD</td>
<td>No need for dosage adjustment for CrCl ≤ 50 mL/min; 400 mg PO BID if CrCl 15–29 mL/min; 600 mg PO QD if CrCl ≤ 10 mL/min</td>
</tr>
<tr>
<td>Didanosine</td>
<td>If weight ≤ 60 kg, 400 mg PO QD; if weight &gt; 60 kg, 250 mg PO QD</td>
<td>For CrCl of 30–49 mL/min, capsule of 200 mg every 48 h or solution of 120 mg every 24 h; for CrCl of 15–29 mL/min, capsule of 150 mg every 48 h or solution of 80 mg every 24 h; for CrCl ≤ 10 mL/min, capsule of 125 mg every 72 h or solution of 50 mg every 24 h</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg PO QD for weight ≤ 75 kg; 240 mg (24 mL) PO QD for weight &gt; 75 kg</td>
<td>For CrCl of 30–49 mL/min, capsule of 200 mg every 48 h or solution of 120 mg every 24 h; for CrCl of 15–29 mL/min, capsule of 150 mg every 48 h or solution of 80 mg every 24 h; for CrCl ≤ 10 mL/min, capsule of 125 mg every 72 h or solution of 50 mg every 24 h</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>If weight ≤ 60 kg, 300 mg PO QD; if weight &gt; 60 kg, 150 mg PO QD</td>
<td>For CrCl of 30–49 mL/min, capsule of 150 mg every 48 h or solution of 100 mg every 24 h; for CrCl of 15–29 mL/min, capsule of 100 mg every 48 h or solution of 60 mg every 24 h; for CrCl ≤ 10 mL/min, capsule of 75 mg every 48 h or solution of 25 mg every 24 h</td>
</tr>
<tr>
<td>Stavudine</td>
<td>If weight ≤ 60 kg, 40 mg PO BID; if weight &gt; 60 kg, 30 mg PO BID</td>
<td>For CrCl of 30–49 mL/min, capsule of 200 mg every 48 h or solution of 120 mg every 24 h; for CrCl of 15–29 mL/min, capsule of 150 mg every 48 h or solution of 80 mg every 24 h; for CrCl ≤ 10 mL/min, capsule of 125 mg every 72 h or solution of 50 mg every 24 h</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300 mg PO QD</td>
<td>For CrCl of 30–49 mL/min, 300 mg every 48 h; for CrCl of 10–29 mL/min, 600 mg every 72 h or 300 mg twice weekly; for CrCl ≤ 10 mL/min, 600 mg every 7 days or HD*</td>
</tr>
<tr>
<td>Tenofovir plus emtricitabine</td>
<td>1 tablet PO QD</td>
<td>For CrCl of 30–49 mL/min, 1 tablet PO QD every 48 h; for CrCl of 15–29 mL/min, 1 tablet PO QD every 72 h; for CrCl ≤ 15 mL/min, 1 tablet PO QD every 96 h or solution of 60 mg every 24 h or HD*</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>300 mg PO QD</td>
<td>For severe renal impairment or HD*, 100 mg TID or 300 mg QD</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse-transcriptase inhibitor</strong></td>
<td></td>
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</tr>
<tr>
<td>Delavirdine</td>
<td>400 mg PO TID</td>
<td>No dosage adjustment necessary for patients not requiring HD</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg PO QD, 1 tablet PO QD</td>
<td>No dosage adjustment necessary; Atripla not recommended if CrCl ≤ 50 mL/min</td>
</tr>
<tr>
<td>Efavirenz-tenofovir-emtricitabine</td>
<td>600 mg PO QD, 1 tablet PO QD</td>
<td>Atripla not recommended if CrCl ≤ 50 mL/min</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg PO BID</td>
<td>No dosage adjustment necessary for patients not requiring HD</td>
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<tr>
<td><strong>Protease inhibitor</strong></td>
<td></td>
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<tr>
<td>Atazanavir</td>
<td>300 mg PO QD</td>
<td>No dosage adjustment necessary for patients not requiring HD</td>
</tr>
<tr>
<td>Darunavir</td>
<td>600 mg Plus 100 mg ritonavir PO BID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>1400 mg PO BID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg PO every 8 h</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Lopinavir-ritonavir</td>
<td>400–100 mg PO BID or 800–200 mg PO QD OD for treatment-naive patients only</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>1250 mg PO BID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600 mg PO BID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Saquinavir soft gel cap</td>
<td>1200 mg TID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>500 mg PO BID; with ritonavir, 200 mg PO BID</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td><strong>Entry inhibitor</strong></td>
<td></td>
<td></td>
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<tr>
<td>Enfuvirtide</td>
<td>90 mg Subcutaneously every 12 h</td>
<td>The recommended dose is based on the use of efavirenz, nevirapine, or efavirenz-experienced patients only</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>The recommended dose varies on the basis of concomitant medications and use of CYP3A inhibitors; patients with CrCl &lt; 50 mL/min should receive a reduced dose</td>
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<tr>
<td><strong>Integrase inhibitor</strong></td>
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<tr>
<td>Raltegravir</td>
<td>400 mg BID</td>
<td>No dosage adjustment necessary</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from US Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents (61). Atripla, efavirenz-emtricitabine-tenofovir; BID, twice per day; CAPD, continuous ambulatory peritoneal dialysis; CCR, creatinine clearance rate; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, hemodialysis; HD*, dose after HD; PO, orally; QD, every day; TID, 3 times per day.
efavirenz in ART-naive patients during 144 weeks of treatment [38]. Adverse renal events did not develop in a subgroup analysis of blacks in these 2 trials [39]. In the Development of Antiviral Therapy trial, which exclusively comprised patients from Uganda and Zimbabwe, 2469 (74%) of the 3316 enrolled patients received first-line ART with tenofovir and zidovudine-lamivudine. The overall incidence of severe reduction in GFR was low (1.6%), and no difference in renal safety endpoints was detected between the regimens [40].

Decreases in GFR in tenofovir-treated patients have been reported. In the Johns Hopkins Cohort, GFR decreased to a greater extent in tenofovir-treated patients than in non–tenofovir-treated patients (19 vs. 11 mL/min), an effect restricted to treatment-experienced patients [41]. Treatment-experienced patients could be more sensitive to adverse effects of tenofovir, more likely to experience adverse drug interactions, or more likely to develop kidney disease because of advanced HIV disease and its attendant comorbidities. The HIV Outpatient Study compared the renal outcomes of 593 tenofovir-treated subjects and 521 HAART-treated subjects who did not receive tenofovir. Tenofovir was associated with a small but statistically significant decrease in GFR, but only 1.1% of tenofovir-treated patients discontinued the drug because of adverse renal events [42].

Area under the curve for tenofovir is increased when it is combined with ritonavir-boosted PIs. One explanation has been that boosted PIs increase tenofovir’s nephrotoxic potential by competing for the same renal transporters, thus impairing its tubule secretion, but recent studies do not support such a mechanism [43]. In 1 study involving ~140 subjects, a tenofovir-boosted PI regimen was associated with a 7–10 mL/min greater decrease in GFR over 48 weeks, compared with a tenofovir–nonnucleoside reverse-transcriptase inhibitor or non–tenofovir-containing regimen [44]. A higher proportion of tenofovir-treated patients in that report were treatment experienced, which perhaps contributed to those observations. In another study, 53 patients treated with tenofovir and boosted atazanavir after multiple prior treatment failures experienced a 7.8 mL/min decrease in GFR over 48 weeks [45], but control individuals were not studied. In an observational study of 445 tenofovir-treated patients observed for a mean of 13 months, GFR decreased a mean of 7 mL/min, and 2% of patients experienced a decrease in GFR to <60 mL/min. Concurrent use of didanosine or amprenavir increased the risk of a decrease in GFR [46]. Again, the change in GFR in non–tenofovir-containing regimens was not reported.

Several reports support the renal safety of tenofovir-boosted PI regimens. When tenofovir was coadministered with either atazanavir-ritonavir or lopinavir-ritonavir in heavily treatment-experienced patients, the rate of drug discontinuation attributable to renal disease was 1.3% [47]. A similar rate of drug discontinuation (1%–2%) was observed when lopinavir (800 mg) plus ritonavir (200 mg) once per day was compared with 400 mg/100 mg twice per day and when fosamprenavir-ritonavir was compared with atazanavir-ritonavir, all in combination with tenofovir-emtricitabine [48, 49]. In the CASTLE Study—which compared atazanavir-ritonavir at 300 mg/100 mg once per day with lopinavir-ritonavir at 400 mg/100 mg twice per day, both with fixed-dose tenofovir-emtricitabine—the rate of adverse event–related drug discontinuations was low (2% and 3%, respectively) [50]. The impact of a potential interaction between boosted PIs and tenofovir was specifically analyzed in the HIV Outpatient Study cohort by comparing renal function in 300 tenofovir-treated patients who received either nonnucleoside reverse-transcriptase inhibitors or boosted PIs (atazanavir or lopinavir). The 12-month intrapatient change in rate of creatinine clearance was not different between groups [51].

Data on the safety of tenofovir among patients with CKD is very limited. A small historical case series of 13 persons with CKD (median creatinine level, 1.7 mg/dL; median creatinine clearance, 56 mL/min; median GFR, 49 mL/min/1.73 m²) who received tenofovir for a median of 13 months showed a confirmed increase in National Kidney Foundation stage in 2 persons [52]. Eleven of 13 patients received an inappropriately high daily dosage of tenofovir, but limited median 12-month changes in creatinine clearance level or GFR were observed (+2.9 mL/min and +3.7 mL/min/1.73 m², respectively). Several patients had significant improvement in measured renal function.

All of these data show low absolute rates of drug discontinuation caused by renal dysfunction (0%–2%) or no differences in severe renal adverse events when tenofovir-containing regimens are compared with regimens not containing tenofovir [53–55]. GFR can decrease 7–10 mL/min over the course of 1 year in tenofovir-treated patients, but in most studies, the increase in serum creatinine level was too small to be identified as clinically significant (~0.05 mg/dL), GFR remained in the normal range, and the rate of drug discontinuation was not greater for patients who received tenofovir. If the decrease in GFR were to continue for many years, it would have serious clinical implications, but no such trend has been reported. These data underscore the importance of carefully screening patients for preexisting renal disease, of following recommendations for appropriate dosage adjustments in patients with renal impairment, and of closely monitoring patients for changes in renal function. From the renal safety perspective, it would be prudent to seek an alternative and equally effective agent for patients who initiate ART with impaired kidney function (GFR, <60 mL/min), although other safety issues must also be considered.
TREATING HIV-INFECTED PATIENTS WITH CKD

Kidney function should be assessed according to existing Infectious Diseases Society of America guidelines [28]. All patients should have a screening urinalysis and a calculated estimate of GFR. Those at high risk for kidney disease (i.e., those with black race, CD4+ count <200 cells/mm³, HIV RNA levels >4000 copies/mL, diabetes, hypertension, or coinfection) should be screened annually to detect subtle changes over time. The standard urinary dipstick is a sufficient screen for proteinuria, but diabetic patients must be tested for microalbuminuria, defined as urinary albumin excretion of 30–300 μg/mg creatinine, a range not detected using conventional dipsticks [56]. Microalbuminuria in diabetic patients predicts subsequent decreases in GFR, and treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers is indicated [57]. Microalbuminuria in nondiabetic patients has been linked to future cardiovascular events [58], a risk that may be modified by angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers [59]. Several issues warrant further study when considering routine testing for microalbuminuria in non-diabetic patients with HIV infection: the reproducibility of the measurements, their proper timing (before or after initiation of ART), and proven benefits of long-term treatment with angiotensin-converting enzyme inhibitors or receptor blockers.

The general approach to diagnosing the cause of kidney disease is to seek reversible causes. Information obtained through the patient history and physical examination should be supplemented by a urinalysis to quantify protein excretion and to test for urinary cells and casts, as well as a renal sonogram to assess kidney size and structure. Additional testing should be individualized (figure 1). A kidney biopsy should be strongly considered for patients with unexplained kidney disease, especially those with heavy proteinuria or reduced GFR, because they are at the greatest risk of ESRD. It is difficult to predict which disease may be affecting the kidneys on clinical grounds alone, although in 1 center, HIVAN was considerably more common when viral load was >400 copies/mL, whereas diseases such as hypertension, diabetes, or classic focal segmental glomerulosclerosis were more common when viral load was <400 copies/mL [60]. A special circumstance for a kidney biopsy exists when seeking the diagnosis of HIVAN in a HAART-naive patient with kidney disease, particularly when ART would not otherwise be warranted because of a CD4+ T cell count >350 cells/mm³. Ongoing viral replication is directly responsible for the renal disease in HIVAN, and ART is recommended, irrespective of CD4+ T cell count, because it preserves kidney function and improves survival [5, 61, 62].

For most patients, the most effective approach to CKD treatment is effective medical management of diabetes and hypertension. Blood pressure should be monitored at each office visit, and antihypertensive treatment should be targeted to a blood pressure <130/80 mm Hg [63]. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are the drugs of first choice, because they reduce urinary protein excretion [57] and slow the progression to ESRD (figure 2). Beta-blockers or non-dihydropyridine calcium channel blockers are alternatives, but their metabolism can be blocked by PIs. Most patients with hypertension and diabetes will require at least 2 antihypertensive medications to achieve optimal control of blood pressure [64].

Glycemic control is critically important in delaying the progression of diabetic nephropathy. The American Diabetes As-

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Figure 1. A simplified algorithm for diagnosing and treating chronic kidney disease (CKD)
Figure 2. Relationship between achieved blood pressure controls and decreases in glomerular filtration rate (GFR) in clinical trials of diabetic and nondiabetic renal disease. HTN, hypertension; MAP, mean arterial blood pressure. Reprinted from Bakris et al. [64] with permission.

Acknowledgments

We acknowledge Healthmatters Communications for receiving payments from the commercial supporter for research and editorial assistance.

Financial support. This article is derived from a content-development meeting, Renal Considerations in HIV Management (2007). An independent educational grant for this program, including a Continuing Medical Education–certified Web cast, was provided by Gilead Sciences Medical Affairs.

Potential conflicts of interest. J.W. has received consulting and lecture fees from Gilead Sciences. T.H. has received consulting and/or speaker fees from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Merck, Monogram Bioscience, Pfizer, and Tibotec. L.S. has received consulting fees from Ortho Biotech Clinical Affairs, Gilead Sciences, Fresenius Medical Care, Kureha, Affymetrix, and Acoligix; lecture fees from Nabi Biopharmaceuticals, Fresenius Medical Care, GlaxoSmithKline, Gilead, Genzyme, Abbott, Amgen, and Ortho Biotech; and grant support from Ortho Biotech Clinical Affairs, GlaxoSmithKline, Pfizer, and Genzyme. C.W. has received grant support from the Gilead Foundation and lecture fees from Gilead Sciences and Roche. B.Y. has been a consultant to Bristol-Myers Squibb, Cerner Corporation, Gilead Sciences, GlaxoSmithKline, Hoffman-LaRoche, Merck, Monogram Bioscience, Pfizer, and Vertex Pharmaceuticals; has served on the speakers’ bureau for GlaxoSmithKline, Merck, and Monogram Bioscience; and has received grant and/or research funding from Bristol-Myers Squibb, Cerner, Gilead Sciences, GlaxoSmithKline, Hoffman-LaRoche, and Merck. G.D.; no conflicts.

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