Highly active antiretroviral therapy (HAART) has changed the natural progression of human immunodeficiency virus (HIV) infection significantly, and opportunistic diseases have become less common, along with declining mortality. More than 50% of deaths in HIV-infected patients receiving HAART are now related to conditions other than AIDS. Approximately 6% of HIV-infected patients develop 1 or multiple episodes of acute kidney injury (AKI), and 15% of patients have evidence of chronic kidney disease (CKD) with a prevalence of HIV-1-associated end-stage renal disease (ESRD) as high as 38% in some inner city hospitals in the United States.

The association between HIV and renal disease was first reported in 1984. The extended survival in HIV patients has been accompanied by the growing emergence of CKD in this population, commonly referred to as HIV-associated nephropathy (HIVAN), and subsequent ESRD as major causes of morbidity and mortality. HIVAN almost exclusively affects African American patients with advanced HIV-1 disease. It is characterized by glomerular capillary collapse, tubular microcyst dilatation, and tubuloreticular inclusions, and if left untreated, it almost uniformly progresses to ESRD within weeks to months. The 2011 US Renal Data System Annual Data Report on CKD in the general population cited a prevalence of CKD of approximately 15.1%. Kidney disease is most likely associated with age older than 60, diabetes, hypertension, and cardiovascular disease. The prevalence of CKD disease in HIV patients is close to that of the general population; the difference lies in the age of the affected patients. The majority of CKD patients in the general population are older than 60, but approximately 96% of HIV patients in the US are younger than 60, with the majority (78%) between the ages of 20 to 50.

**PATHOGENESIS AND RISK FACTORS OF HIVAN**

Many theories exist as to cause of CKD in HIV patients. Classic HIVAN results from direct infection by HIV-1 and expression of viral genes in renal...
The predominant affliction of African Americans is highly suggestive of genetic susceptibility in the development of CKD. The complex interplay between genetics, viral factors, and host response factors that result in the unique phenotype of HIVAN is not yet entirely understood. Antiretroviral therapy can contribute to renal dysfunction directly by inducing acute tubular necrosis, acute interstitial nephritis, crystal nephropathy, and renal tubular disorders or indirectly via drug interactions. Additionally, as survival is prolonged in HIV patients, CKD may arise from traditional etiologies, such as aging, male sex, hypertension, smoking, and diabetes.

Several challenges arise in patients with HIVAN, including lack of awareness of kidney disease, identification of early signs and symptoms, or collaboration between nephrologists and HIV specialists. The earlier the disease is detected, the sooner preventive and treatment strategies can be implemented to preserve kidney function.

It is important to identify HIV patients at risk for developing CKD, and common risk factors that are associated with HIVAN are listed in Table 1. To demonstrate the progression of HIVAN, we include a patient case (sidebar) and discuss patient factors associated with HIVAN. During this hospital admission, the patient had a urinalysis that showed elevated urine protein level of 100 mg/dL with urine albumin to creatinine ratio of 1,100 mg/g. The patient has several risk factors, including low CD4 count, hypertension, proteinuria, and low glomerular filtration rate (eGFR < 90 mL/min).

Additionally, the consequence of exposure to nephrotoxic drugs on the development of kidney disease is still controversial. Non-antiretrovirals commonly used by HIV patients, such as amphotericin B, cidofovir, foscarin, pentamidine, and high-dose acyclovir, have known nephrotoxic potential. Acyclovir, ciprofloxacin, foscarin, and sulfonamides can cause intratubular precipitation of crystals, leading to AKI.

DISEASE PROGNOSIS

Kidney disease is strongly associated with increased mortality risk among HIV-infected patients. A study of 2,038 HIV-infected women demonstrated an association between proteinuria and elevated serum creatinine (SCr) levels, with an increased incidence of death and the development of an AIDS-defining illness. In a similar study, Gardner et al reported that renal laboratory abnormalities were associated with an increased risk of death and hospitalization in a cohort of 885 HIV-infected women.

The most striking finding on renal biopsy is collapsing focal glomerulosclerosis, but all renal compartments are essentially affected. If left untreated, HIVAN carries a poor prognosis and invariably leads to ESRD within months. Prior to the ultimate fruition of HAART, the median survival for HIV patients with ESRD is 13 months, compared with 38 months for non–HIV patients undergoing maintenance dialysis.

TREATMENT

Despite scientific advancements in understanding the pathogenesis of HIVAN, current recommendations...
for beneficial treatments are largely based on observational data and uncontrolled trials.15

**HAART**

HIV-related ESRD has dramatically declined,9,16 and several case reports have suggested substantial benefits documenting clinical and histologic improvement after initiation of HAART.17-19 A case report of a 37-year-old African American man describes his hospital course beginning from admittance with an SCr of 8.71 mg/dL and a calculated creatinine clearance (CLcr) of 7 mL/min, leading to the requirement for hemodialysis (HD). During this admission he was diagnosed with HIV-1, and a percutaneous kidney biopsy showed changes characteristic of HIVAN. HAART was initiated in the patient 1 week before HD. After 13 weeks of treatment and 12 weeks of HD, a repeat percutaneous kidney biopsy showed glomeruli recovery. Fourteen weeks after stopping dialysis, his SCr recovered to 1.49 mg/dL and serum HIV-RNA was less than 500 copies/mL.17 Chemlal et al18 and Betjes et al19 reported similar cases of substantial improvement in the course of biopsy-proven HIVAN after introduction of HAART.

A larger prospective cohort of 3,976 HIV-1-infected individuals aimed to assess sequential changes in the incidence of HIVAN and the association with HAART. Over a 12-year study period, 94 patients developed HIVAN. HAART was associated with a substantial reduction in HIVAN incidence, with the risk of developing HIVAN reduced by 60% (95% CI, -30 to -80%) among patients using HAART. No patient developed HIVAN when HAART was initiated before the development of AIDS.20 In another analysis, patients with biopsy-proven HIVAN or other HIV-related renal diseases receiving a protease inhibitor–based treatment regimen had a slower rate of decrease in CLcr compared with those who either did not receive antiretrovirals or only received a regimen of nucleoside analogues (0.08 vs 4.3 mL/min per month; \( P = 0.04 \)). This study suggests a potential benefit from protease inhibitors on the progression of these nephropathies, but the small study group of 16 HIV patients followed for a median of 16.6 months retrospectively limits the study’s generalizability.21

Not only is HAART therapy effective in treating established HIVAN, it may also potentially reduce the incidence of de novo HIVAN. Dosing adjustment for some HAART medications may be required, depending on stage of CKD. Table 2 provides a list of HAART medications that may need dose adjustments based on individual renal function, and practitioners should refer to a drug information database for specific recommendations. No particular HAART regimen is recommended over another, and unfortunately, some patients will still ultimately progress to ESRD regardless of appropriate HAART.20 The patient in this case study is receiving HAART.

### Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) have demonstrated efficacy in slowing the progression of kidney disease in the general population.22 Some of the beneficial effects of ACEIs are associated with improved renal hemodynamics, reduced proteinuria, and cytokine modulation.10 For all these reasons, ACEIs have been suggested for use in patients with HIVAN. A case-control study23 compared the course of 18 patients with biopsy-proven HIVAN on time of renal survival. Nine patients were treated with captopril, while 9 controls were identified by matching age, race, gender, and SCr level. Renal survival was enhanced in the captopril-treated patients compared with the controls (mean renal survival, 156 ± 71 days vs. 37 ± 5 days; \( P < 0.002 \)).23

In a similar focused prospective study24 at a single center, a cohort study with 44 patients examined the long-term effects of ACE inhibition on

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<th>Table 2. HAART Medications with Recommendations for Dose Adjustment in Patients With CKD10</th>
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renal survival in HIVAN. A total of 28 patients received fosinopril, and 16 patients were controls. Median renal survival of treated patients was 479.5 days, with only 1 patient developing ESRD. All untreated controls progressed to ESRD, with a median renal survival of 146.5 days ($P < 0.0001$).24

Neither study identified nor controlled for the use of specific HAART, therefore any potential benefits that may have been achieved from antiretroviral therapy are unknown. Additional research is warranted to assess HAART with or without concomitant ACE inhibition on the progression of HIVAN. Despite the limitations of these studies, they still suggest that ACEIs may be beneficial in curbing progression of HIVAN and that this class of drugs is a reasonable first choice as antihypertensive agents.

The optimal intensity of ACEI therapy, the potential effects of angiotensin-receptor blockers (ARBs), and the specific benefits of ACEIs on HIV-related kidney diseases other than HIVAN are unknown. The National Kidney Foundation K/DOQI guidelines suggest that it is reasonable to initiate an ACEI or ARB as first-line therapy for HIV-infected patients with hypertension and proteinuria.22 Additionally, the Infectious Disease Society of America (IDSA) guidelines for management of CKD in HIV patients recommend that, in patients with evidence of nephropathy, initial blood pressure control with the use of an ACEI or ARB is preferred for those patients with proteinuria.10 A patient who has hypertension, proteinuria, and some degrees of CKD might benefit from an ACEI or ARB therapy.

**Corticosteroids**

Several studies support the use of corticosteroids in treating HIVAN by demonstrating significant improvements in renal function and proteinuria. In a prospective trial aimed at determining if prednisone improves the course of HIVAN, 20 patients with HIVAN were enrolled to receive treatment with prednisone at a dose of 60 mg/day for 2 to 11 weeks, followed by a tapering course of prednisone over a 2- to 26-week period. The majority of patients (17/20) had improvements in both renal function and proteinuria. Twelve of 13 tested patients showed a reduction in 24-hour urinary protein excretion, with an average decrease from 9.1 ± 1.8 g/day to 3.2 ± 0.6 g/day ($P < 0.005$). Five patients relapsed after prednisone was discontinued, but they then improved in response to the second course of prednisone.25

A concern arises with the potential immune effects corticosteroids may produce that can affect the HIV course in patients. A randomized, double-blinded,
placebo-controlled trial by McComsey et al suggests that short-term prednisone therapy given in addition to antiretroviral therapy for HIV infection is relatively safe and does not predispose to severe infection. A total of 41 patients with baseline median CD4 cell count of 131x10⁶ cells/l (85% had a history of opportunistic infection) were enrolled in the trial. All but 1 patient received a stable antiretroviral regimen for a median of 158 days, including 36 patients taking a protease inhibitor. Patients were randomized to 8 weeks of prednisone 0.5 mg/kg daily or placebo. Prednisone decreased immune activation (plasma tumor necrosis factor α levels and CD38+CD8+ cells decreased significantly) without effects on HIV-1 RNA levels or CD4 cell counts. The study concluded that short-term prednisone administration is well tolerated and reasonably safe in advanced HIV-1 disease.

The combination of HAART with prednisone therapy has not been studied in patients with HIVAN specifically. IDSA guidelines recommend considering prednisone therapy in patients with HIVAN whose kidney function declines despite use of HAART and who are without active infection or active illicit injection drug use. Recommended dosing for prednisone in HIVAN is 1 mg/kg of body weight per day for 2 months, followed by a 2- to 4-month taper.

**Dialysis**

The progression of HIVAN to ESRD can occur rapidly and may require dialysis therapy. Additionally, overall survival rates among HIV-infected ESRD patients on dialysis have been improving since the advent of HAART, and rates are now similar to non-HIV patients on dialysis. Renal replacement therapy can be safely delivered to HIV-infected patients, and there is no difference in predicting survival in HIV-infected patients with ESRD when comparing HD and peritoneal dialysis.

**Renal Transplant**

Historically, transplantation was not commonly available to HIV-patients because of risks of immunosuppression with respect to the viral disease. However, the use of effective antiretroviral therapy has reported mixed outcomes in case reports and series in HIV-infected renal-transplant recipients. In a recent study of 150 kidney transplantations in HIV-infected patients, both patient- and graft-survival rates were high at 1 and 3 years after transplant, with rates falling between those reported in the national database for older kidney-transplant recipients (≥ 65 years) and those reported for all kidney-transplant recipients. A higher-than-expected rejection rate was observed at 1 and 3 years after transplant, raising a serious concern and implicates the need for better immunotherapy. HIV infection remained well controlled, with stable CD4+ T-cell counts and no increases in complications associated with HIV infection. Renal transplantation may be considered for patients with ESRD if provided in a supervised clinical trial or at centers with adequate experience in this area.

**DISCUSSION**

The case patient’s HIV infection is well controlled with the current HAART regimen; however, the regimen does not contain a protease inhibitor that may have beneficial effects on CKD progression. At this time no changes to the HAART regimen were made, but the provider needs to continue to monitor medications—valacyclovir, sulfamethoxazole-trimethoprim, HAART medications (eg, zidovudine, lamivudine)—and kidney function. The patient is only taking amlodipine for hypertension, which is moderately well controlled, ranging from 110-147/74-92 mmHg. Before discharge lisinopril was added for CKD, hypertension, and proteinuria.

HIVAN is a complex medical condition with multiple factors, including progression of disease, complexity of the medication regimens, side effects, viral resistance, compliance issues, social issues, and other factors. As the survival rate of HIV-infected patients extends, the focus of management continues to shift toward management of chronic diseases, such as CKD. Practitioners should collaborate with other HIV specialists, nephrologists, and other health care providers to establish the best and safest care for patients. Practitioners also can stay current on HIV-related topics at www.hivguidelines.org and follow infectious disease societies (eg, IDSA) for the latest recommendations as emerging data become available.
CONCLUSION
The prevalence of HIVAN is anticipated to continue increasing because of the disproportionate number of African American individuals afflicted with HIV. Despite the growing significance of HIVAN in the HIV-infected population, there is a dearth of evidence to support current therapeutic options. Further research is needed into the genetic basis of the racial predilection of HIVAN, its pathogenesis, and new treatments.

References

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