

NEPHROLOGY

Rounds®

Update on HIV-associated Nephropathy

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Since its discovery 25 years ago, the human immunodeficiency virus (HIV) has become a worldwide pandemic. In the United States (US) alone, over a million persons were living with HIV and the acquired immunodeficiency syndrome (AIDS) at the end of 2003.¹ Based on statistics provided by the World Health Organization (WHO), an estimated 39.5 million people worldwide are living with HIV.² Despite prevention efforts, the rate of new infections is stable in the US and in most regions of the world. In 2006, there were 4.3 million new infections worldwide.² Although highly active antiretroviral therapy (HAART) has resulted in dramatic improvements in morbidity related to HIV, many contemporary studies indicate that kidney disease is an increasingly frequent complication of HIV infection.^{3,4} HIV-associated nephropathy (HIVAN) is the most common form of kidney disease found in the HIV-infected population.⁵ It is a unique clinical and pathological entity thought to be secondary to direct HIV infection of renal cells.⁶⁻⁸ This issue of *Nephrology Rounds* assesses the importance of HIVAN in the era of HAART, with a focus on the epidemiology and treatment of this disease.

Clinical manifestations

Patients with HIVAN typically present late in the natural history of their HIV disease with nephrotic-range proteinuria and significant renal dysfunction. HIVAN usually occurs in the setting of poorly-controlled HIV infection marked by low CD4⁺ T cell counts and elevated viral loads.^{9,10} However, HIVAN can be part of the initial manifestation of HIV infection and has been reported during primary HIV infection (within 6 months of infection),^{11,12} as part of the acute HIV syndrome,¹³ or with undetectable viral loads.^{6,11} Despite the common finding of severe proteinuria and hypoalbuminemia, most patients with HIVAN do not have significant edema or hypertension.^{14,15} The lack of clinically-evident signs on physical examination may contribute to the late presentation of these patients to healthcare providers. The reasons for these observations are unclear, but salt wasting related to HIVAN or alterations in oncotic pressures due to increased serum immunoglobulin may be possible mechanisms.^{16,17}

A definitive diagnosis of HIVAN can only be made by kidney biopsy (Table 1). Characteristic pathologic findings of HIVAN include collapsing focal segmental glomerular sclerosis (FSGS) with podocyte hypertrophy in areas of collapse (Figure 1). Lymphocytic infiltration and fibrosis may be observed in the interstitium. Tubular changes feature dilated microcysts filled with proteinaceous casts and atrophied tubular epithelial cells. It is likely that the severe glomerular and tubular injury is responsible for the rapid decline in renal function found in HIVAN, which is rare in other forms of FSGS. Immunofluorescence is non-specific. Endothelial tubulo-reticular inclusions related to plasma interferon levels have been reported on electron microscopy and are now thought to be an infrequent finding due to the efficacy of HAART.

HIV-infected patients have more autoantibodies compared with HIV-negative patients, but these abnormalities are rarely associated with clinically-apparent disease. Several studies have reported the prevalence of autoantibodies in HIV-infected patients and detected cryoglobulinemia in 17%-42%, rheumatoid factor in 19%-60%, antinuclear antibodies in 0%-23%, anticardiolipin antibodies in 10%-94%, and antinuclear cytoplasmic antibodies in 12%-23%.¹⁸⁻²² Furthermore, in the US, up to 30% of patients with HIV may be co-infected with hepatitis C virus (HCV).²³ The presence of HCV infection or positive serologies may confuse the diagnosis of HIVAN and lower a clinician's threshold to perform a kidney biopsy. Generally, the urine sediment in HIVAN may reveal hyaline casts, but is typically bland. On renal ultrasound, kidneys are commonly enlarged and echogenic, corresponding to the classic

AS PRESENTED IN THE ROUNDS OF
THE NEPHROLOGY DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
BOSTON, MASSACHUSETTS



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Table 1: Common clinical and pathological findings in HIVAN

| Pathologic findings | Clinical findings |
|---|--|
| Light microscopy: Glomerular changes Collapsing focal segmental glomerular sclerosis "Pseudocrescents" Tubular changes Microcystic dilatation Flat, atrophied tubular epithelium Interstitial changes Lymphocytic infiltrate Interstitial fibrosis Immunofluorescence: Nonspecific pattern Electron microscopy: Tubuloreticular inclusions | Physical findings: Minimal elevations in blood pressure Minimal peripheral edema Laboratory: Nephrotic range proteinuria Significant renal dysfunction Hypoalbuminemia Bland urine sediment False positive auto-antibodies Elevated HIV RNA and low CD4 counts Renal ultrasound: Normal or large echogenic kidneys |

histologic findings of proliferation, lymphocytic infiltration, and tubular dilatation. However, low CD4 counts in the presence of nephrotic syndrome or normal-sized kidneys on ultrasound are not sufficient to rule-out HIVAN and, therefore, these findings usually warrant kidney biopsy for a definitive diagnosis.^{24,25}

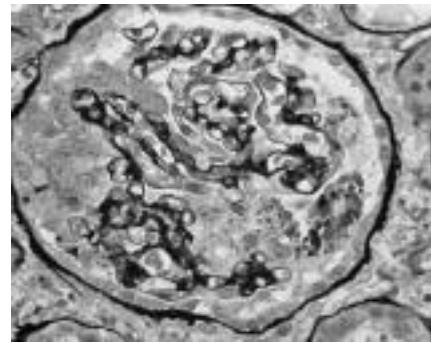
Epidemiology

Among patients with HIV, prevalence estimates for chronic kidney disease (CKD) range from 7.2%-32.6% and primarily vary according to the racial composition of the study population.^{10,26-29} Although these studies use different criteria to define renal failure, all report a high prevalence of renal abnormalities. In the multicenter Women's Interagency HIV Study (WIHS),¹⁰ 32.6% of patients had proteinuria $\geq 1+$ on dipstick analysis. In the HIV Epidemiology Research Study (HERS), 7.2% of participants were found to have renal disease at baseline, with 14% of patients subsequently developing renal insufficiency after a mean observation time of 21 months.^{29,30}

Although these studies provide overall estimates for CKD in the HIV-infected population, the true prevalence of HIVAN is unknown because the kidney biopsies required for a definite diagnosis are performed relatively infrequently. Ahuja et al designed a screening protocol to determine the prevalence of HIVAN in a cohort of 557 HIV-infected adults. Diagnostic biopsies were performed in patients with >1.5 g/day proteinuria. HIV-associated nephropathy accounted for 71.0% of diagnoses and was found to occur exclusively in black patients with a prevalence of 3.5%.³¹ An autopsy study in Texas found the overall prevalence of HIVAN to be 6.9% (27 of 389 autopsies) with a prevalence of 12.0% in blacks.

In the US black population aged 20-64 years, HIVAN is the third most common cause of end-stage renal disease (ESRD) after diabetes and hypertension, and accounts for approximately 9% of new cases.³² Although the incidence of ESRD has been stable since 1997, the prevalence of

Figure 1: Characteristic histopathologic findings of HIV-associated nephropathy Light micrograph with silver stain demonstrates focal segmental glomerulosclerosis with collapse of the glomerular tuft



ESRD due to HIVAN has climbed steadily due to improved survival among HIV-infected patients. The total number of patients with ESRD secondary to HIVAN in the US Renal Data System (USRDS) doubled between 1995 and 2000. Nonetheless, these figures likely underestimate the true burden of HIV in this group, since many renal networks do not report the diagnosis of HIV in order to protect patient confidentiality. Despite the problem of under-reporting, Eggers and Kimmel estimated that patients with HIV still have a 10-fold greater risk of developing ESRD compared with the general population.³³

Racial predilection of HIVAN

The predilection of HIVAN for black patients is widely recognized. The first reported cases of HIVAN were described in 1984, in a group of 11 black patients in New York City with AIDS.³⁴ Since then, numerous case series have revealed that the majority of ESRD cases related to HIV occur in young black men.^{11,35-37} Dialysis registry data have provided the most convincing evidence for the marked racial disparity in HIVAN. Based on the USRDS, 90% of all cases of ESRD due to HIV occur in blacks.³⁸ Case series from other parts of the world have also revealed a preponderance of HIVAN in black patients. Kidney biopsy studies from France, Brazil, and Thailand have confirmed this remarkable susceptibility to HIVAN in HIV-infected patients of African descent.³⁹⁻⁴²

Blacks are the largest and fastest growing racial group with HIV in this country (Figure 2). In 2004, half of all new HIV infections in the US were among blacks, who represent only 15% of the overall US population.¹ In view of these demographic trends and the excess risk of HIVAN among blacks, it has been projected that the size of the HIV-infected ESRD population will continue to rise.⁴³ Based on mathematical models of the HIV epidemic formulated from recent data generated by the Centers for Disease Control and Prevention (CDC) and the USRDS, the prevalence of ESRD due to HIV is expected to increase dramatically in the future because of the burgeoning population at risk.⁴³

Figure 2: Blacks are now the predominant demographic group living with HIV/AIDS

Since most ESRD patients with HIV are black, the prevalence of ESRD among HIV-infected patients is expected to steadily increase.

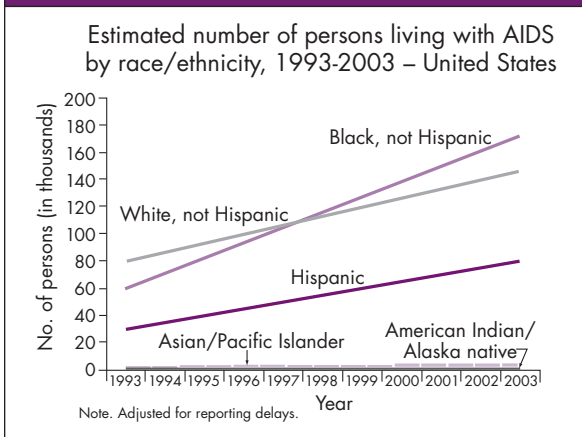


Figure courtesy of the CDC.¹

The importance of HIVAN in the black population may extend to the larger population of HIV-infected individuals living in Africa. The WHO reported that in 2006, 24.7 million persons (63% of all persons with HIV-infection) were living with HIV in sub-Saharan Africa.² As a result, kidney disease may grow in importance in this region of the world, particularly since HAART is provided to these countries and disease patterns increasingly resemble those in the US.

Prognosis

In the earliest case histories prior to the HAART era, patients with HIVAN inexorably progressed to ESRD within weeks to months.^{34,36,37} However, subsequent cohort studies indicated that the natural history of this disease likely depends on the severity of both underlying kidney disease and HIV-infection at the time of presentation.^{10,44} Risk factors for the progression of HIVAN to ESRD include low CD4⁺ T cell count, low creatinine clearance, HCV co-infection, and high HIV ribonucleic acid (RNA) level.^{40,44,45}

Kidney disease is associated with striking increases in mortality risk among HIV-infected patients. Szczech et al demonstrated an independent association between proteinuria and elevated serum creatinine (SCr) levels with mortality.²⁶ In this study, proteinuria (defined by a dipstick reading of $\geq 2+$ on urinalysis) and an elevated SCr level (≥ 1.4 mg/dL) were associated with an increased risk of death due to all causes (hazard ratio 2.5; $P < .0001$) after controlling for predictors of AIDS-related death, including CD4 lymphocyte count, HIV RNA level, and the use of HAART.²⁶ The relative hazard for death in this population was greater in those with proteinuria and CD4⁺ T cell counts of $\leq 500/\text{mm}^3$ versus those who had CD4⁺ T cell counts of $\leq 350/\text{mm}^3$ without proteinuria. Similarly, in a cohort of 885 HIV-infected women, Gardner and colleagues reported that renal laboratory abnormalities were associated with an increased risk of death and hospitalization.^{29,46}

Recommendations for screening for kidney disease

In recognition of the growing burden of renal disease in the HIV population, the Infectious Disease Society of America (IDSA) recently issued guidelines specifically for CKD management in HIV-infected patients.⁵ Based on the finding that HIV is a risk factor for developing CKD and the strong prognostic significance of kidney disease in this population, these guidelines recommend screening for kidney disease using a urine analysis and a calculated estimate of renal function upon diagnosis of HIV. Patients with risk factors for CKD (eg, black race, CD4⁺ T cell counts $< 200/\text{mm}^3$, or HIV RNA levels > 4000 copies/mL, diabetes, hypertension or HCV co-infection) should undergo annual screening.⁵

Treatment

Early in the course of the HIV epidemic, the overall incidence of ESRD due to HIV increased annually prior to the introduction of HAART. Since 1995, after protease inhibitors (PI) came into use, the incidence of ESRD secondary to HIV/AIDS declined and then stabilized.³ Since then, a growing number of observational studies have provided further support for HAART as a treatment for HIVAN. Other treatment options that may influence the course of HIVAN include angiotensin-converting enzyme inhibitors (ACEIs) and steroids (Table 2).

Antiretroviral therapy

The Strategies for Management of Antiretroviral Therapy (SMART) study has provided important insights into the value of HAART in treating HIV-related kidney disease. In this study, 5,472 HIV-infected patients who had a CD4⁺ T cell counts of $> 350/\text{mm}^3$ were randomly assigned to continuous or episodic use of HAART and were followed for a mean of 16 months. Compared with continuous HAART, investigators found that planned treatment interruptions guided by CD4⁺ T cell counts significantly increased the risk of opportunistic disease and death from any cause. In addition, the investigators found an increased risk for fatal or nonfatal ESRD (hazard ratio [HR] 4.5, 95% confidence interval [CI], 1.0–20.9) in the treatment-interruption arm. Although this study was not statistically powered to detect a difference in renal outcomes, the high incidence of ESRD in the treatment-interruption group suggests that HAART and sustained viral suppression are important factors in preventing and slowing the progression of kidney disease.

The efficacy of HAART as a treatment for HIVAN has been characterized primarily by observational studies, since the demonstrated survival benefit associated with HAART has rendered randomized, controlled, clinical trials in this area unethical. Several case series have suggested that HAART has a beneficial effect on renal dysfunction. A cohort of 53 patients with biopsy-proven HIVAN from the Johns Hopkins renal clinic were found to have better renal survival when treated with HAART compared with those who did not receive HAART (adjusted HR 0.30, 95% CI, 0.09–0.98). In a retrospective study of 19 patients with a clinical diagnosis of HIVAN,

Table 2: Treatment of HIV-associated nephropathy (HIVAN)

| Treatment | Comment | Level of evidence |
|---|--|--|
| Highly active antiretroviral therapy (HAART) | Considered first-line therapy for HIVAN. | Nonrandomized intervention studies Retrospective cohort studies Dramatic results from case reports |
| Corticosteroids | Indicated in the setting of deteriorating renal function despite HAART. | Nonrandomized intervention studies Retrospective cohort studies |
| Angiotensin-converting enzyme (ACE) inhibitors | Reasonable first choice as an antihypertensive agent. | Nonrandomized intervention studies Retrospective cohort studies |
| Dialysis | HIV-infected patients achieve survival equivalent to the HIV-negative dialysis population. | Retrospective cohort studies |
| Kidney transplantation | Preliminary results indicate graft survival is comparable to the general population. | Preliminary results from an NIH-sponsored multicenter trial Nonrandomized intervention studies |

after a median follow-up of 16.6 months, a significant association between PI use and a slowing in the decline of creatinine clearance was found compared with those who did not receive PIs.⁴⁷ Finally, in a case report, a patient with HIVAN and dialysis-dependent renal failure became dialysis free after 15 weeks of HAART. Repeat renal biopsy revealed significant histologic recovery of fibrosis with only infrequent glomeruli showing mild collapse and minimal fibrosis.¹¹ Based on these data and the understanding that HIV infection itself appears to be the cause of HIVAN, IDSA guidelines recommend HAART as first-line therapy for HIVAN.⁵ HAART is recommended in this setting irrespective of other indications for treatment of HIV, such as level of CD4⁺ T cell count or HIV RNA level.

ACE inhibitors

Angiotensin II increases the cellular synthesis of transforming growth factor- β (TGF- β) that has been implicated in the pathogenesis of HIVAN.⁴⁸ As a result, ACEI have been proposed as a logical therapy for HIVAN to reduce the production of TGF- β . In a study of 18 patients with HIVAN, 9 were treated with captopril, while 9 controls were identified by matching for age, race, gender, and level of SCr concentration.⁴⁹ Renal survival was enhanced in the captopril-treated group compared with controls (mean renal survival, 156 \pm 71 days versus 37 \pm 5 days, $P < 0.002$). In a single-center, prospective, cohort study of 44 patients with HIVAN, 28 patients received fosinopril 10 mg/day, and 16 were followed as controls.⁵⁰ Median renal survival of treated patients was 479.5 days, with only one patient developing ESRD. All untreated controls progressed to ESRD, with a median renal survival of 146.5 days ($P < 0.0001$). Despite the limitations of these studies, they 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.

Steroids

Several observational studies support the use of steroids in treating HIVAN.^{45,51,52} Smith et al prospectively enrolled 20 patients with HIVAN to receive treatment with corticosteroids. Most patients (17/20) had improvements in kidney function or a reduction in 24-hour urinary protein excretion with an average decrement from 9.1 \pm 1.8 g/day to 3.2 \pm 0.6 g/day ($P < 0.005$).⁵³ Another study of steroid therapy employed a control group and found similar results with no increased risk of infection in the steroid group.⁵² Steroids are considered second-line therapy for patients with HIVAN and are indicated in those who have deteriorating kidney function despite HAART. Prednisone may be given at 1 mg/kg of body weight per day for 2 months followed by a 2-4 month taper.

Dialysis

The last two decades have seen an expansion in the number of patients with HIV receiving dialysis. Prior to the advent of HAART, early studies reported that patients with ESRD and HIV initiating dialysis died after 1-3 months.⁵⁴ More recent studies based on the USRDS have demonstrated a gradual improvement in survival among HIV-infected patients on dialysis.^{4,55-57} By 1999, the 1-year survival of HIV-infected patients was equivalent to the general population (240 deaths per 1000 patient-years among HIV-infected individuals versus 236.4 deaths per 1000 patient-years in the general population).⁴ A study comparing survival patterns in France found similar mortality rates between the French Dialysis in HIV/AIDS cohort and the French Dialysis Outcomes and Practice Patterns Study II.⁵⁸ Outcomes are thought to be equivalent on hemodialysis or peritoneal dialysis.⁵⁵

Preparation for renal-replacement therapy should begin with a kidney transplant evaluation in patients with well-controlled HIV infection and an estimated

glomerular filtration rate (eGFR) <25 mL/min per 1.73 m² (see kidney transplantation section below).⁵⁹ Early surgical referral for placement of a native arteriovenous (AV) fistula is also preferred because inferior outcomes for AV grafts appear to be magnified among HIV-infected patients.⁶⁰⁻⁶³ Various studies have demonstrated that AV fistulae in HIV-infected patients have similar survival rates compared with HIV-negative controls. However, AV grafts in HIV-infected patients have worse thrombosis-free survival and higher infection rates compared with HIV-negative patients.

Kidney transplantation

HIV infection should no longer be considered an absolute contraindication to kidney transplantation. Multiple studies have demonstrated that HIV-infected kidney transplant recipients have patient and graft survival rates that are comparable to the general population.⁶⁴⁻⁶⁶ Although episodes of acute rejection have been frequent, there have been few graft losses. Despite the understandable concern that the immunosuppression required to prevent graft rejection would accelerate the progression of HIV, only 3 cases of opportunistic infections or neoplasms after transplantation have been reported in the published literature.⁵⁹ In general, CD4⁺ T cell counts and HIV RNA levels have remained stable despite complicated drug interactions and HAART dosing alterations with immunosuppressive regimens. The National Institutes of Health is sponsoring an ongoing study of kidney and liver transplantation among HIV-infected individuals in 20 transplant centers across the US (<http://www.hivtransplant.com>, Accessed: August 3, 2007). Preliminary results from this trial have provided further support that kidney transplantation is a viable option for HIV-infected patients. Inclusion criteria for this trial includes CD4⁺ T cell count $\geq 200/\text{mm}^3$ in adults, CD4% $\geq 30\%$ in children aged 1-2 years old, and CD4% $\geq 20\%$ in children aged 2-10 years. For patients taking HAART, HIV RNA must be undetectable using an ultrasensitive assay. Other centers are providing solid organ transplantation to HIV-infected patients on a case-by-case basis.⁶⁷

Conclusions and future directions

As the survival of HIV-infected patients improves, the focus of management continues to shift towards chronic diseases such as CKD. Current epidemiologic trends in HIV infection indicate that the prevalence of HIVAN will continue to rise because of the disproportionate number of black 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 into the genetic basis of the racial predilection of HIVAN, its pathogenesis, and new treatments are needed.

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Disclosure: Drs. Choi, O'Hare, and Rodriguez have no disclosures to declare in association with the contents of this issue.

This activity is supported by an educational donation provided by

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