Renal Diseases Associated with Human Immunodeficiency Virus Infection: Epidemiology, Clinical Course, and Management

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Human immunodeficiency virus (HIV)–associated nephropathy (HIVAN) and other glomerular lesions (e.g., immunoglobulin A nephropathy and immune complex glomerulonephritis) are frequent complications of HIV infection. These renal diseases usually present as a nephrotic syndrome with progressive loss of renal function and an increased risk of mortality. The prevalence and epidemiology of these renal lesions remain largely undefined; however, most studies agree that black race is a major risk factor for HIVAN. Observational studies have suggested that antiretroviral medications and angiotensin-converting enzyme inhibitors have beneficial effects on slowing the progression of renal disease among patients with HIVAN; however, little is known about the effect of these therapies on other renal lesions. Future research should focus on gaining a better understanding of the distribution and determinants of renal disease among HIV-infected patients as well as on performing controlled studies to test treatment strategies.

During the past decade, HIV-infected patients developed end-stage renal disease (ESRD) and began receiving dialysis at a rate that increased by 20% per year [1]. In 1998, the US Renal Data Service reported that HIV-related renal diseases were the fourth leading cause of ESRD among black men aged 20–64 years, with >3700 such patients reported to date [2]. In 1999, HIV-related renal disease became the third leading cause of ESRD in this demographic group [3]. These estimates of the morbidity rate associated with renal disease in the HIV-infected population, although likely affected by underreporting, do not take into account the even larger population of patients with early renal insufficiency. This population of patients with renal disease who have not yet begun to receive dialysis represents an even larger patient group whose size has not been estimated but whose morbidity rates have also increased in relation to their renal disease.

The prognosis for patients with HIV infection and ESRD is poor, with the mortality rate reaching 50% at 1 year after initiation of dialysis [4–8]. Although these studies are limited by their inclusion of patients who were seen in the era before the use of highly active antiretroviral therapy (HAART; pre-1995), current US Renal Data Service data demonstrate a mortality rate that continues to be >30% at 1 year after initiation of dialysis [2]. The rate of incidence of patients living with HIV infection and AIDS continues to rise, with the largest proportionate increase occurring among blacks and among Hispanic women infected through heterosexual contact [9–11]. As the population of HIV-infected individuals grows due to new cases and better survival, an increased number of patients will be at risk for many complications associated with their HIV infection, including renal disease. In spite of the potential beneficial effect of antiretroviral medications on the survival of patients with renal disease [12, 13], projections estimate that the exponential increase in the number of patients who are living with AIDS will result in a similar expansion in the number of patients with HIV infection who have progression to ESRD [14].

HISTOLOGIC LESIONS OF THE HIV-RELATED RENAL DISEASES

Although the most common histologic lesion seen among HIV-
infected patients is HIV-associated nephropathy, a glomerulopathy that demonstrates focal segmental glomerulosclerosis with collapsing features, a spectrum of other histologic lesions is associated with HIV infection. Histologic lesions, such as membranoproliferative glomerulonephritis, minimal change disease, membranous glomerulopathy, amyloidosis, immune-complex glomerulonephritis, and IgA nephropathy, make up as much as one-third of the diagnoses in case series of patients who have undergone renal biopsy [15]. Although a limited understanding of the epidemiology and clinical course of HIV-associated nephropathy (HIVAN) has been established, little is known about the risk factors and natural history of these other HIV-related renal diseases. Care must be taken in research and in clinical practice to avoid assumptions about either the homogeneity or heterogeneity of the natural history of these lesions. This review will focus on what is known about the epidemiology and clinical course of HIVAN.

CLINICAL PRESENTATION AND RISK FACTORS FOR HIVAN

HIVAN usually presents as nephrotic-range proteinuria with a progressive loss of renal function and an interval of <10 months from the time of diagnosis to progression to ESRD [16–20]. These early descriptions suggest that hypertension is not a common feature. Renal ultrasound frequently reveals large, echogenic kidneys [21].

Many reports suggest that black race [16–19, 22–25], Haitian background [26], male gender [18], injection drug use [16–19, 22, 23, 26], and a decreased CD4 cell count [15] are risk factors for the development of HIVAN. Interpretation of these reports is limited by the unknown effects of selection bias introduced through the methods by which patients were identified for inclusion. Several studies have included only those patients who were seen by nephrologists during admissions to the hospital for other diagnoses [17, 19, 22, 23, 25]. Other studies have identified patients for inclusion retrospectively through a review of the results of renal biopsies and autopsies [15, 26] or through a review of billing codes that were based on discharge diagnoses [16, 24]. These methods may select for patients who have a greater severity of disease, those who are of a socioeconomic status that allows for greater access to inpatient health care, or those who have an atypical or aggressive course of disease and thus are more likely to be seen by a nephrologist and undergo biopsy. Because these studies are not population based, they cannot estimate the proportion of the population with HIV infection that is at risk for nephropathy, nor can they accurately quantify the risk within specific subpopulations (e.g., blacks or patients with a history of injection drug abuse).

The largest series that described patients with HIVAN identified patients for inclusion on the basis of their having undergone renal biopsy for clinical evaluation [27]. Although this method may also be affected by selection bias, it is of note that this study demonstrates associations that contradict previous conclusions. The 102 patients who were included in this study had advanced renal disease at the time of biopsy, with a mean serum level of creatinine of 5.4 mg/dL (range, 2.4–8.8 mg/dL). Contrary to the findings of earlier studies that suggested that men are preferentially affected, a substantial number of patients were women (28%). Although 97% of patients were black, a finding that confirmed race as a risk factor, observation of a small number of patients from other racial groups suggested that the diagnosis is not restricted entirely to the black population. Risk behaviors for acquisition of HIV were not limited to injection drug abuse, as previously described [16–19, 22, 23, 26], but instead included patients with histories of homosexual, bisexual, and heterosexual contact. Finally, although the mean CD4 cell count for all patients was 48.5 cells/mm³, >20% patients had a CD4 cell count of >200 cells/mm³ at the time of diagnosis. Although this study provided insight into the determinants of HIVAN, it did not examine the association between the HIV RNA level and the presence of HIVAN.

Given these results, the clinical course and determinants of HIVAN appear to be more heterogeneous than initially described, occurring in both women and men and among patients with various modes of infection. Because of the potential for bias that is introduced by patient selection, no definitive conclusions about the relative risk of nephropathy in association with sex, mode of infection, or other clinical determinants of disease can be made on the basis of findings from many current studies. The study of a large, population-based sample is required to accurately quantify risk among specific subgroups (e.g., women or blacks) and to verify these findings concerning the clinical course of the disease.

RATE OF PROGRESSION OF RENAL DISEASE

Similar to the contradictory evidence that defines risk factors for disease, there is disagreement among studies with regard to the description of the natural history of the nephropathy. Case series that were published during the years that HIVAN was first described demonstrated an almost universal requirement for dialysis within <1 year of diagnosis [20, 28–31]. The interval from diagnosis of disease to progression to ESRD has increased to a median of 8 months [32] and 16.6 months [27] in later studies. Although the time to progression to ESRD within these studies is highly dependent on the degree of renal dysfunction at presentation, a trend toward a slower rate of progression is evident. The reasons for the decline in the rate of progression are not clear and may reflect either earlier diagnosis, advances in the care of HIV-infected patients, or differences in compliance or access to care among study populations. To gain an
understanding of why the time to progression has increased during recent years, the clinical factors that affect disease progression and the potential therapeutic role of antiretroviral medications must be explored.

CLINICAL FACTORS THAT AFFECT DISEASE PROGRESSION

The CD4 cell count at presentation appears to have an association with the diagnosis of HIVAN and the aggressiveness with which it progresses to ESRD. A case series of 10 patients with HIVAN revealed that each patient had a CD4 cell count of <200/mm³ at the time of diagnosis in a group of patients with moderately advanced renal insufficiency at the time of biopsy (median serum level of creatinine, 2.4 mg/dL) [15]. This observation may be interpreted as the nephropathy is a late manifestation of HIV infection, or it may indicate that patients with lower CD4 counts manifest a more aggressive course of disease and may be more likely to require renal biopsy for clinical management of their disease.

Supporting the latter hypothesis is a recent analysis of the Women’s Interagency HIV Cohort Study [33], a longitudinal study of the spectrum and course of the clinical manifestations of HIV infection in women. The Women’s Interagency HIV Cohort Study enrolled >2000 women who were not selected for the presence of renal disease and prospectively followed them to study complications of HIV infection and markers of disease progression. In this population-based study, predictors of progression of renal disease among women with proteinuria included an absolute CD4 cell count of ≤200 cells/μL (hazard ratio, 3.57; P = .001) and a detectable HIV RNA level (hazard ratio, 2.33; P = .02). Although this study was limited by its inability to define histologic lesions and may have included women with HIV-related renal diseases other than HIVAN, it supports the pathobiology that markers of viral replication and immune status may have an impact on the mechanism of the progression of nephropathy. Furthermore, it suggests that these relationships may exist across the spectrum of HIV-related renal diseases, for which few clinical data exist.

TREATMENT

Antiretroviral medications. Consistent with these studies that demonstrate a more aggressive course of disease among patients with decreased CD4 cell counts and increased HIV RNA levels, the deterioration of renal function among patients with HIVAN who are not receiving antiretroviral medications is also rapid [17, 19, 31, 34]. Although reports of the clinical course of the disease vary in association with the severity of renal dysfunction at diagnosis, patients who were not receiving antiretroviral medications in these studies had progression to ESRD within 2–4 months of diagnosis of renal disease.

Several studies have suggested a beneficial effect on slowing the progression of renal disease among a cohort of patients who were receiving monotherapy with zidovudine [31, 35–37], protease inhibitors [32], and HAART [38]. Case series that were published at the same time that HIVAN was first described suggested that therapy with zidovudine resulted in better renal outcomes. Although limited by issues of selection and indication bias as well as by the unknown effects of noncompliance, these studies generated hypotheses regarding the role of antiretroviral medications in the treatment of HIVAN. A 1996 retrospective cohort study by Kimmel et al. [35] demonstrated that the use of a single nucleoside reverse-transcriptase inhibitor (primarily zidovudine) and the use of captopril were independently associated with a longer time to onset of ESRD. Although this study analyzed these effects in a multivariable analysis, its conclusions are limited by the manner in which patients were chosen for inclusion. Patients initially were chosen to receive captopril treatment because they displayed hypertension or nephrotic syndrome, and 9 patients were matched as control patients on the basis of creatinine level, age, race, and sex. Although such issues as hypertension and the amount of proteinuria were incorporated into the analysis, the effects of these indications for treatment with captopril, as well as the effects of antiretroviral medications on the results, are not clear.

Recent case reports and case series now support the beneficial effect of protease inhibitors [32] and HAART [38] on progression of renal disease. Although limited by their study designs and small numbers of patients, these reports continue to suggest a therapeutic effect of aggressive management with the use of antiretroviral agents among patients with renal disease. In one case report, the improvement in renal function was so dramatic in a patient with biopsy-proven HIVAN that the patient was able to discontinue dialysis soon after triple antiretroviral therapy was initiated [38]. Although little is known about the natural history of HIV-related renal diseases other than HIVAN, similar results have been seen among patients with membranous nephropathy. Two HIV-infected patients with membranous nephropathy were reported to have experienced a dramatic reduction in proteinuria after beginning a combination regimen of antiretroviral medications that contained a protease inhibitor [39]. The therapeutic role of antiretroviral agents in patients with HIV-related renal diseases other than HIVAN has yet to be defined.

Study design and potential bias introduced by the indication for treatment limit the conclusions that can be drawn from these studies. Although it cannot be determined from these reports whether this benefit is related to the use of specific medications (i.e., protease inhibitors) or the effective suppression of viral replication by means of HAART, the demonstrated...
benefit of therapy is currently the most effective treatment strategy. This benefit is consistent with the hypothesis that HIVAN in humans involves a direct effect of HIV-1 expression in cells of the kidney [40]. Further investigation of these treatment strategies appears promising.

**Prednisone.** Observational studies have demonstrated an association between improved renal survival among patients with HIVAN and the use of prednisone [27, 32, 41, 42]. Although treatment with prednisone did uniformly improve renal function, relapses in the decline of kidney function did occur, which required repeated therapy, and the risk of opportunistic infections was increased [42].

**Angiotensin-converting enzyme inhibitors.** Finally, observational data further suggest a therapeutic benefit of the use of angiotensin-converting enzyme inhibitors among patients with HIVAN [35, 43]. A prospective cohort study by Burns et al. [43] examined the effect of the angiotensin-converting enzyme inhibitor fosinopril on the progression of HIVAN. This study compared the clinical course of 12 patients with HIVAN who consented to take fosinopril with that of 8 patients who refused treatment. Seven of the 20 patients in the cohort were taking a single nucleoside reverse-transcriptase inhibitor (zidovudine, didanosine, or zalcitabine). The serum levels of creatinine of patients who were receiving fosinopril remained stable during the 12–24-week follow-up period, whereas the creatinine levels of patients who were not taking fosinopril increased from 1.4 mg/dL to 6.4 mg/dL. These results, however, do not control for the benefit seen among patients who were taking antiretroviral medications. Although it is unclear how the antiretroviral agents contributed to the apparent benefit of angiotensin-converting enzyme inhibitors, these results are consistent with those of Kimmel et al. [35] and warrant further investigation.

**EVALUATION AND TREATMENT OF HIV-INFECTED PATIENTS WITH RENAL DYSFUNCTION**

Even among patients with normal kidney function, the presence of proteinuria indicates early glomerular disease. Although no clinical practice guidelines exist regarding the evaluation of the HIV-infected patient with renal dysfunction, it would be appropriate to screen patients for proteinuria via a urine analysis performed at the time of their initial clinical visit. Follow-up examinations of individuals in high-risk groups, such as blacks, may be justified on an annual basis. If proteinuria is present, further evaluation that uses a 24-h urine collection to quantify the amount of protein that is excreted daily would be warranted. In addition, because they are also associated with secondary renal disease, serologic studies to assess the presence of chronic infection with hepatitis B, hepatitis C, and syphilis should also be performed. Because such clinical markers as CD4 cell count, HIV RNA level, and degree of proteinuria do not reliably predict the histologic diagnosis in the HIV-infected patient [15], renal biopsy is frequently required to guide therapy. Indications for biopsy should include those used in other renal diseases, including nephrotic-range proteinuria and progressive loss of renal function in those clinical settings where knowledge of the histologic diagnosis would change clinical therapy.

On the basis of current observational evidence, the use of HAART and angiotensin-converting enzyme inhibitors appears to benefit the patient with HIV-related renal disease by slowing the progression of decline in renal function and decreasing the level of proteinuria. Because the use of prednisone is associated with an increased risk of infectious complications, consideration regarding its use should be given only after these other measures fail to stabilize renal function.

**SUMMARY**

The clinical epidemiology and course of HIVAN have not been fully described. Limitations due to study design have clearly affected the conclusions that can be drawn from available analyses. Although a gap in our understanding of the distribution and determinants of HIVAN exists, even less has been established regarding the other histologic lesions that complicate HIV infection (e.g., IgA nephropathy and immune complex glomerulonephritis). A greater understanding of the risk factors for, mechanism of, and clinical modifying factors for HIV-related renal diseases is essential. Only through the use of population-based studies, the increased utilization of renal biopsy to define renal histologic lesions, and the testing of treatment strategies in a prospective, controlled manner will significant progress be made toward minimizing the morbidity and mortality associated with the renal complications of HIV infection.

**References**
