Are We Missing an Epidemic of HIV-Associated Nephropathy?1

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ABSTRACT
HIV-associated nephropathy is infrequently cited as a common cause of ESRD. It is likely, however, that by the end of the decade, HIV-associated nephropathy will be the third leading cause of ESRD in African Americans between the ages of 20 and 64. Underreporting for reasons of confidentiality and a failure to track this specific diagnostic category nationally may account for the nephrology community's inattention. As a result of this community's failure to define this issue, national agencies are poorly prepared to recognize and anticipate the changing demographics of the AIDS epidemic as it affects the practice of nephrology. The study presented here concluded: that a national registry should be created to track the incidence of HIV-associated nephropathy as a cause of ESRD; that renal biopsies should be routinely performed to confirm the clinical diagnosis of HIV-associated nephropathy; that anonymous serological screening of all patients and health care providers in dialysis units be reconsidered in order to maintain vigilance for potential unit outbreaks; that the National Institutes of Health and the Office of AIDS Research be better appraised of the importance of this issue by the nephrology community; and that special attention be directed toward the underlying cause(s) of HIV-associated nephropathy and the cofactor(s) that determine the predilection of this disease in blacks.

Key Words: HIV-associated nephropathy, renal failure, ESRD, AIDS, HIV-1

As a nephrology community, are we failing to recognize that by the end of the decade, HIV-associated nephropathy (HIVAN) will be one of the leading causes of kidney failure in African Americans from 20 to 64 years of age? In this review, we will summarize the current knowledge of the clinical characteristics, natural history, and epidemiology of HIVAN, and, based on current trends, make some projections about what can be expected in the future.

The association between chronic glomerular disease and AIDS was first reported in 1984 by Rao and associates, who described a group of AIDS patients with focal segmental glomerulosclerosis and nephrotic-range proteinuria (1). The GFR of these patients fell rapidly, terminating in end-stage renal failure within 8 to 16 wk. Mortality was extremely high, approaching 100% within 6 months of diagnosis. That same year, Pardo and associates also described five patients with heavy proteinuria, who had died of AIDS (2); these patients were found to have renal lesions that histologically resembled those lesions reported by Rao. When considering the criteria for the diagnosis of AIDS at that time, it is not surprising that these first reports of AIDS-related nephropathy were characterized by a dismal clinical course. Before the discovery that HIV type 1 (HIV-1) caused AIDS, the diagnosis was defined by the presence of opportunistic infections (most commonly Pneumocystis carinii pneumonia) and/or Kaposi's sarcoma occurring in patients with no obvious predisposing cause (3). As a result, patients only met the criteria for HIVAN very late in the course of HIV-1 infection and only after the presentation of clinical AIDS.

By 1984, the CDC had recorded slightly more than 3000 cases of AIDS resulting in nearly 1300 deaths. In New York City, the mortality rate was approaching 70% and the median survival time for all patients with AIDS was between 4 and 10 months (4,5). Because of the rapid progression of AIDS, particularly late in the course of HIV-1 infection, the early experience with AIDS complicated by renal failure focused justifiably on the ethical dilemma of initiating renal replacement therapy in patients with a universally high and rapid mortality (6-8). Because the diagnosis of HIVAN now includes patients with early seroconversion, increasing numbers of patients with this diagnosis have been identified who have a much better prognosis (9).

HIVAN must be viewed in the context of the overall epidemic (10-12). The AIDS epidemic is not under control and the incidence of infection continues to rise. In the United States, between 850,000 and 1,200,000 people are infected with HIV-1; worldwide, 10 million people are infected. Homosexual and bisexual men continue to be the major groups at risk, with
prevalence rates ranging from 20 to 70%. Homosexual men in San Francisco have the highest HIV-1 prevalence (70%). The prevalence of HIV-1 infection in intravenous drug users is only slightly less and varies by geographic region. In New York and northern New Jersey, the prevalence is 50 to 60%, with rates decreasing to <5% in nonmetropolitan areas outside the East Coast.

AIDS is now the leading cause of death for black and Hispanic men aged 25 to 44, and it is the second leading cause of death for similarly aged black women. For whites of similar age, AIDS is the second leading cause of death for males and sixth leading cause of death for females. The largest proportionate increase in new AIDS cases is now found in black and Hispanic women who acquire the disease through heterosexual contact. Thus, AIDS is no longer confined to the homosexual community and intravenous drug users (13–15).

Renal disease can present as a complication at any time in the course of HIV infection. As depicted in Figure 1, HIV-1 infection has a protracted clinical course (16). There is a clinical “latent” period, varying between 8 and 10 yr., which precedes the development of opportunistic infections. Although patients are asymptomatic, there is no true viral latency and active viral replication and high rates of CD4 cell destruction and turnover can be detected even during clinical latency (17,18). At any time during the course of HIV-1 infection, certain AIDS-related syndromes may develop, including Kaposi's sarcoma, neurologic disease (AIDS dementia complex), gastroenteropathy, and nephropathy (HIVAN). The onset of these manifestations does not correlate strictly with CD4 cell depletion or immunosuppression per se. Furthermore, the poor correlation between these syndromes and viral burden suggests that other predisposing factors may be equally important, such as strain specificity in AIDS dementia complex (19–21) or cofactors such as herpesvirus for Kaposi's sarcoma (22). Whether similar factors play a role in the pathogenesis of HIVAN remains to be determined.

Between 1984 and 1992, almost 300 cases of chronic renal disease associated with HIV-1 infection were reported (1,2,8,23–32). Of these, 50%, or 150 patients, had a clinical course and biopsy that was consistent with the diagnosis of HIVAN. Typical features of HIVAN include enlarged kidneys, microcystic tubule dilation, tubulointerstitial inflammation, interstitial edema, and fibrosis (Figure 2). Glomerular involvement is usually focal and segmental, with glomerulosclerosis, collapse of the glomerular tuft, and hypertrophy of visceral epithelial cells. Endothelial cells containing tubuloreticular inclusions are often reported but are a nonspecific finding (33,34). The etiologic role of HIV-1 in this disease is supported by the observation that transgenic mice expressing HIV-1 envelope and regulatory proteins develop a renal phenotype that is essentially identical to the disease in man (35,36). Almost 90% of the cases of HIVAN occur in blacks, and the cofactors responsible for this racial predilection remain unknown.

Blacks are disproportionately affected by the HIV epidemic and are also at greater risk in general for the development of renal disease. The new acquisition rate of AIDS in black women is nearly 15 times that of white women, and the new acquisition rate in black men is five-fold higher than that for whites. Blacks...
Figure 2. Histopathology of human HIVAN. A kidney from a patient showing an obsolescent glomerulus (arrowhead), dilated tubules occupied by proteinaceous casts (asterisk), and an area of interstitial fibrosis. Another glomerulus shows segmental glomerular sclerosis with reactive glomerular epithelial cells. (By Rappaport et al.; used with permission from Kidney International, volume 46, page 16, 1994).

Comprise almost 90% of subjects with HIVAN. The prevalence of HIVAN nationally is population-dependent and variable: it is relatively low when the population studied is predominantly white and homosexual, and relatively high when the population studied is predominantly black (23,26,37,38). In the Northeast, glomerular disease occurs in 10 to 15% of patients with AIDS.

Whereas the majority of HIV-1 infected patients with renal disease have features typical of HIVAN, patients with HIV-1 infection are also at risk of developing many other forms of renal disease (2,8,26,30,31). Of those HIV-positive patients without typical HIVAN, mesangial hyperplasia is the most common form of renal disease; other forms of acute and chronic glomerulonephritis are the next most common. Several HIV-positive patients have been described as having an acute proliferative, crescentic glomerulonephritis of the IgA type with a polyclonal gammopathy, circulating immune complexes, and cryoglobulinemia (39-41). Finally, acute renal failure is often a complicating factor in patients with HIV-1 infection and patients may be predisposed to acute tubular necrosis from intravascular volume depletion (42).

Although the syndrome of HIVAN is being recognized more frequently, our understanding of its natural history is incomplete. Because the diagnosis must be confirmed by kidney biopsy, clinical studies have suffered from the lack of distinction between HIVAN and other forms of chronic kidney disease. The outcome of patients with HIVAN is determined primarily by the stage of HIV infection. Overall, the rate of progression to renal failure tends to be rapid, with a median time of 10 weeks from initial evaluation to dialysis (27). Individual rates of progression may be quite variable, and some patients have had a gradual progression over years. When asymptomatic seropositive patients are included, the diagnosis of HIVAN can precede the need for hemodialysis by 1 yr or longer (43).

The survival time of patients with HIVAN is poor. Furthermore, the prognosis for patients with HIVAN is worse than that of other forms of renal disease. Recent reports suggest, however, that the prognosis may be improving (44,45). Although this may be true, much of the reported change in the survival time has been a function of the change in diagnostic criteria. In the mid-1980s, few patients with HIVAN and AIDS lived longer than 6 months. Because the diagnostic criteria for HIVAN now include seropositivity without clinical AIDS, patients appear to be surviving longer, although this may be artifactual. Once an AIDS-defining condition develops, such as severe CD4 cell depletion, opportunistic infection, or dementia, survival time is usually measured in months with or without dialysis. Again, these data reflect the overall condition of the patient rather than the addition of renal disease as a superimposed poor prognostic sign. The median survival time for HIVAN patients who are seropositive but asymptomatic is 9.7 months; for HIVAN patients with generalized lymphadenopathy and constitutional symptoms (previously AIDS-related complex) the median survival time is 3.6 months, and for HIVAN patients with AIDS, the median survival time is 1.9 months (27). Anecdotal cases of patients with AIDS surviving on dialysis for substantially longer periods have been reported (43). From these survival time data, two conclusions can be reached: (1) survival time of patients with HIVAN is determined predominantly by the clinical stage of HIV-1 infection; and (2) HIVAN clearly confers additional and independent risk to patients at all stages of HIV-1 infection.

The clinical course is similar for patients with ESRD who subsequently seroconvert while on dialysis. These patients do not have HIVAN but, instead, have HIV-1 infection complicating preexisting renal failure. Again, in this group of patients, the stage of HIV-1 infection is the primary determinant of the outcome. Patients whose seroconversion is first documented when they present with an AIDS-defining condition have a worse prognosis (average survival time, 122 days) than those patients who are found to have seroconverted while they are asymptomatic (average survival time, 600 days) (43). Like patients with...
HIVAN, the survival time of ESRD patients who seroconvert is determined predominantly by two factors: (1) the clinical stage of HIV-1 infection; and (2) the additional risk of ESRD. Thus, patients who are seropositive have a higher mortality while on dialysis than patients who are seronegative. Furthermore, patients who are seropositive with renal disease have a higher mortality than patients who are seropositive without renal disease. These data suggest that renal disease and/or dialysis may adversely alter the natural history of HIV-1 infection and possibly hasten the progression to AIDS in seropositive individuals by a mechanism that remains unclear.

The importance of HIVAN in the United States in the ESRD patient population is unclear, but as a renal community, we have failed to recognize and educate ourselves about its magnitude. As a reflection of our failure, the Office of AIDS Research Planning at the National Institutes of Health has only recently noted HIVAN as a noteworthy independent complication of AIDS (in 1994) and has assigned this disease a very low priority. Considering the magnitude of the AIDS epidemic and the potential problem for the ESRD population, we need to act quickly to address this issue. Unfortunately, specific tracking of this disease is lacking on the national level and we can only extrapolate information from various databases.

As a cause of kidney failure, HIVAN is increasing in incidence, but its true incidence is currently unknown. The diagnostic codes submitted to the Health Care Financing Administration (HCFA) to determine Medicare eligibility at the onset of ESRD serve as the traditional source of incidence data for all forms of kidney disease, but with HIVAN there may be considerable underreporting because of concerns about patient confidentiality. In 1988, a task force on AIDS and kidney disease projected that as many as 10,000 to 15,000 persons would likely develop renal disease as a consequence of AIDS, and recommended the development of a national registry for HIV-positive patients with kidney disease (46). This was not done. Despite the potential for errors resulting from underreporting, the data from the United States Renal Data System (USRDS) demonstrate that the incidence of HIVAN as a cause of kidney failure has more than tripled since 1990. In their 1993 annual report, the USRDS identified 297 cases of AIDS-related nephropathy as the primary cause of ESRD between 1987 and 1990 (47). These data were updated in the 1995 report to reflect 916 cases occurring between the years 1989–1992 (48). For blacks aged 20 to 65, HIVAN was the sixth leading cause of ESRD, nearly as common as lupus nephritis (Figure 3). These data likely underestimated the magnitude of the problem because of poor tracking of the diagnosis nationally.

In New York state, unlike the national registries, HIVAN has been closely tracked by the ESRD Network #2 since 1986 (Figure 4). Between 1989 and 1992, 387 new cases were reported in New York state alone (49). According to the Centers for Disease Control and Prevention, 21% of the approximately 40,000 blacks reported nationally as having AIDS live in New York State (14), and of the national total of HIV-positive patients receiving hemodialysis, 15 to 20% per year have been treated in New York since 1991 (50–52). Assuming that the distribution of AIDS is the same as the distribution of seropositivity, and that the same national percentage of black patients who are HIV-positive develop HIVAN, New York would account for 20 to 25% of the national total of patients at risk for HIVAN. This should provide a reasonably accurate analysis of the incidence of HIVAN. There should have

Figure 3. Incidence of primary disease as a cause of ESRD in blacks aged 20 to 64, 1989 to 1992 (adapted from USRDS 1995 Annual Data Report, Reference 48). Hypertension and diabetes account for the majority of cases (35% and 33%, respectively), with "other" as the third leading category (15%). Underreporting of HIVAN would likely appear in this category. HIVAN accounted for just 2% of the cases nationally, with 40% of the cases from New York state, where tracking of this disease is more accurate.
been 1500 to 2000 cases of HIVAN occurring in the United States between 1989 and 1992, not the reported 916. Applying the recent New York incidence rate of 120 to 150 cases of HIVAN per year to the national total, we could expect to see 480 to 750 new cases of HIVAN per year. A similar figure is derived by analyzing the number of HIV-positive patients who are receiving hemodialysis nationally. This number has risen on an average of 20% per year since 1989 (50), so that almost 2800 patients were being treated as of 1993. If, as a conservative estimate, 50% of these individuals have HIVAN with a median survival time of 12 months, it is likely that 700 patients with HIVAN are beginning hemodialysis each year. If these estimates are correct, HIVAN is the fourth leading cause of ESRD among blacks between the ages of 20 to 64, only slightly behind hypertension, diabetes, and chronic glomerulonephritis. To determine whether this predicted incidence is valid, we have reviewed our experience in an urban patient population at Mount Sinai Hospital during the past 3 yr (1992 to 1994). Of the 325 new patients entered into our chronic dialysis program, 8% had HIVAN diagnosed either by biopsy or by the rapid progression to renal failure with heavy proteinuria in patients who were HIV-seropositive. In young black adults, HIVAN accounted for 20% of newly diagnosed ESRD and it has become the third leading cause of ESRD in this group, after hypertension and diabetes. Few nephrologists who care for urban patients that are predominantly black or Hispanic would be surprised by this suggestion, despite the national registry data.

The incidence of HIV-1 infection and HIVAN is rising faster than the 4 to 7% age-adjusted increase incidence of chronic renal failure from other causes in blacks (47,48,53). Most of this increase can be attributed to hypertensive, diabetic, and other kidney diseases (including HIVAN), because the incidence of chronic glomerulonephritis, cystic disease, and lupus nephritis has remained relatively constant. Should the incidence of HIVAN continues to rise at its present rate of 20% per year, by the year 2000, it will account for 20% of all ESRD among young black patients (Figure 5). It is possible that the increase in incidence of HIVAN may be even greater as patients with HIV infection live longer.

It is imperative that we begin to address this issue as a community, and we suggest the following steps be taken:

1. We must develop a national registry to track the incidence of HIVAN as a cause of ESRD, separate from other diagnostic categories, and to follow its natural history once dialysis is initiated.
2. For accurate diagnosis, renal biopsies should be performed to confirm clinical suspicion. Several reports indicate that the diagnosis cannot be made on clinical grounds alone (2,23,27,54).
3. As a community, we should provide accurate data regarding the evolving epidemiology of this disease to the National Institutes of Health and the Office of AIDS Research so that appropriate priority can be assigned for clinical and basic research.
4. We should consider banking serological specimens on a regular basis from all dialysis patients and health care providers. Although there have been no reported outbreaks of HIV in dialysis centers in this country, it is clear that when established standards are not followed (55,56), outbreaks may occur (57). Serologic banks will facilitate rapid investigation into outbreaks, should they occur.
5. Finally, special attention should be directed to-

Figure 4. Incidence of HIVAN in New York state (adapted from Neff and Rasmussen, Reference 49). A 30% to 50% annual increase has occurred since 1989, with an annual incidence now estimated at 120 to 150 patients.
ward the underlying cause(s) of HIVAN and the cofactor(s) that determine the predilection of this disease for blacks. The results of such studies will likely have an important impact not only on HIVAN, but on other causes of FSGS in blacks.

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