The Early Years: AIDS and AIDS Nephropathy in the Early 1980s

This year marks the 25th anniversary of the first published report of AIDS, a series of five cases of Pneumocystis carinii pneumonia in healthy young men with male sexual partners (1). In the subsequent year, more than 450 cases were reported to the Centers for Disease Control (2), and the recognized population at risk was expanded to include injection drug users (3) and hemophiliacs (4). The syndrome was formally defined as AIDS by the Centers for Disease Control in September 1982 (5), although the pathogenesis remained unclear. Reports of transfusion-related (6) and maternal-fetal transmission (7) supported an infectious etiology, and the identification of cases in female sexual partners of men with AIDS suggested a role for heterosexual transmission (8). In early 1983, investigators at the Pasteur Institute reported the isolation of a new retrovirus from a patient with early signs of AIDS (9). The next year, researchers at the National Cancer Institute confirmed the presence of a previously isolated human T cell leukemia virus (HTLV-III) in peripheral lymphocytes from patients with AIDS (10,11) and subsequently cloned the retrovirus that now is known as HIV-1 (12).

In 1984, there were several reports of a unique and rapidly progressive form of focal sclerosing glomerulosclerosis (FSGS) in patients with AIDS (13–15). The characteristic glomerular "collapse" was actually first described in uninfected patients (16), but the collapsing FSGS that is associated with HIV is distinguished by the presence of microcystic tubular dilation and interstitial inflammation (17). Although "HIV-associated nephropathy" (HIVAN) was initially described in the setting of advanced AIDS, it was soon recognized that FSGS could also precede the clinical symptoms of AIDS (18). As more cases were reported, it also became apparent that HIVAN primarily affected patients of African descent (18,19). Studies suggested that HIV-1 might infect the kidney or cells within the kidney in HIVAN (20,21), but definitive evidence for renal epithelial infection by HIV-1 did not come until 2000 (Figure 1) (22). Despite the rapid progression to ESRD and death among patients with HIVAN (18), kidney disease received relatively little attention compared with AIDS-defining opportunistic infections and malignancies in the first 10 yr of the epidemic.

A Period of Progress: Scientific Advances in HIV-1 and HIVAN, 1985 to 2006

The late 1980s and 1990s were marked by rapid progress in the field of HIV. The US Food and Drug Administration approved the first commercial test for HIV-1 infection in 1985 and the first antiretroviral agent, zidovudine, in 1987. Two additional nucleoside reverse transcriptase inhibitors were approved by the Food and Drug Administration in 1991, prompting discussion of combination therapy. With the approval of the first protease inhibitor in 1995, combination regimens, or highly active antiretroviral therapy (HAART), quickly became the standard of care, with dramatic reductions in AIDS-related mortality (23). Despite the optimism prompted by these improvements in survival, scientists began to consider the implications of possible reservoirs for HIV-1 replication in the central nervous system and in mononuclear cells (24–26). In 1997, scientists identified a viral reservoir in memory T cells (27) and demonstrated HIV-1 replication in lymph nodes in the setting of undetectable plasma viral load (28). The recognition that HIV infection could not be eradicated with available therapy prompted new interest in long-term complications of HIV infection and antiretroviral therapy, including metabolic disorders and liver and kidney diseases.

During this period of progress, optimism, and disappointment in the study of HIV, laboratory investigators also gained significant insights into the pathogenesis of HIVAN. In 1991, investigators at the National Institutes of Health described a transgenic mouse model of HIV-1 infection (Tg26) that developed kidney disease that was identical to human HIVAN (29). The Tg26 mouse model expresses a gag/pol-deleted HIV-1 transgene and is the basis for much of our current understanding of HIVAN pathogenesis. Reciprocal transplantation of kid-

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neys between Tg26 and wild-type mice demonstrated that viral gene expression in the kidney is required for the development of HIVAN (30). Serial deletion of HIV genes from the Tg26 model identified specific viral genes, nef and vpr, which are involved in the pathogenesis of HIVAN (31,32). An HIV-1 transgenic rat model also develops kidney disease that resembles HIVAN and may provide another resource for future studies (33,34).

Targeted expression of viral genes in lymphocytes and lymphoid tissue has been shown to recapitulate some but not all of the pathologic findings that are observed in the Tg26 mouse model and in human HIVAN, suggesting that HIV-1 gene expression in both renal and nonrenal tissues may play a role in the development of HIVAN (32,35). More recently, the development of HIVAN in a mouse model with podocyte-selective expression of HIV-1 suggests that expression in the glomerular epithelium is sufficient (36) but does not exclude a synergistic role for HIV gene expression in nonrenal tissues. In this model, murine genetic background also affects the development of kidney disease. Similar observations in the Tg26 mouse model, which demonstrates significant variability in renal phenotype when bred onto different genetic backgrounds, led to the identification of a genetic susceptibility locus on mouse chromosome 3 (37). These animal data are consistent with the clinical observation that host genetic factors clearly play an important role. HIVAN occurs almost exclusively in patients of African descent (18,19,38,39), and patients with ESRD secondary to HIVAN are more likely to have a family history of ESRD (40).

A Global Epidemic of AIDS-Related Renal Disease: Epidemiology of HIV-1 and HIVAN in the HAART Era

With the widespread introduction of HAART in 1996, there was a dramatic decline in AIDS-related deaths in the United States (23). The proportion of deaths that are attributable to AIDS-defining conditions has continued to decline, with chronic complications such as liver and kidney disease becoming increasingly important contributors to mortality in the HAART era (41). At the same time, there has been a more subtle decrease in the incidence of ESRD related to HIV, which reached a plateau at approximately 800 to 900 new cases per year in the United States (Figure 2) (42). Survival among HIV-infected dialysis patients has also improved in the HAART era, approaching survival rates in the general ESRD population (43). On the basis of these data and the increasing prevalence of HIV infection among susceptible black individuals, the pool of patients who are at risk for developing HIVAN has expanded dramatically. Mathematical models that take into account both the expanding population and the impact of HAART in decreasing the incidence of HIVAN in susceptible individuals predict a substantial increase in the number of HIV-positive ESRD patients in the United States (Figure 2) (42).

In sub-Saharan Africa, where an estimated 25 million people are living with HIV/AIDS (44), expanding access to antiretroviral therapy will improve survival and may also be accompanied by an epidemic of HIVAN. Cross-sectional data from

Figure 1. In situ hybridization for HIV-1 mRNA in kidney biopsies. (A and B) Kidney biopsy from an HIV-negative patient demonstrating no HIV-1 mRNA in the sense control (A) or the antisense (B) hybridization of a serial section. (C and D) Kidney biopsy from an HIV-positive patient with kidney disease. No hybridization was observed in the sense control (C). Antisense hybridization (D) demonstrates HIV-1 mRNA in the cytoplasm of tubular epithelial cells and in cellular casts (CC) in the tubular lumen (TL) but not in protein casts (PC). Magnifications: ×125 in A and B; ×60 in C and D.
South Africa demonstrate albuminuria in 7% of patients, with a surprisingly high prevalence of biopsy-proven HIVAN in patients with microalbuminuria (45). In a series of 99 consecutive kidney biopsies in HIV-infected black South Africans, 27% were diagnostic of HIVAN (46). Cross-sectional data from 195 HAART-naïve Ugandans revealed that 43% had a creatinine clearance <50 ml/min, and 21% had dipstick proteinuria (47), whereas the median creatinine clearance in 90 HAART-naïve Nigerian patients was <60 ml/min (48). In a cohort of 740 HAART-naïve Rwandan women, the prevalence of proteinuria was as high as 13% in women with a CD4 cell count <200 (49). Preliminary data from 3313 patients who are enrolled in a randomized antiretroviral trial in Uganda and Zimbabwe demonstrate stabilization or slight improvement in kidney function after the initiation of HAART (50). These studies suggest that antiretroviral therapy improves renal function, possibly because of underlying HIVAN. Of note, all of these studies used the Cockcroft-Gault equation to estimate GFR, raising the possibility that malnutrition and low body weight may have biased the estimates. Neither of the currently accepted estimation equations has been well validated in HIV-positive patients, and neither has been evaluated in an African population. With expanding access to HAART, including potentially nephrotoxic agents, the accurate estimation of kidney function in this population will be an important challenge.

Treatment and Prevention of HIVAN in 2006
Despite remarkable scientific progress in elucidating the pathogenesis of HIVAN, current recommendations for treatment are largely based on observational data and uncontrolled trials. The decline in the incidence of HIV-related ESRD after the introduction of HAART strongly suggests a role for antiretroviral therapy in the treatment of HIVAN (42), which is further supported by reports of clinical and histologic improvement after the initiation of HAART (51,52) and by retrospective cohort studies (53,54). The efficacy of HAART is also consistent with the pathogenic role of direct HIV infection in the development of HIVAN (22). Until recently, the adjunctive use of corticosteroids was not supported by known pathogenic mechanisms, although uncontrolled studies have suggested some improvement in the clinical course of HIVAN (55–57). Recent in vitro data demonstrate a potential role for inflammatory mediators in the tubulointerstitial compartment (58), providing some scientific rationale for the use of corticosteroids in active disease. Support for the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is extrapolated from evidence of benefit in other proteinuric kidney diseases, with limited data in HIVAN (59,60).

Although the introduction of HAART has had a significant impact on the epidemiology of HIV-related kidney disease, antiretroviral therapy seem to be only partially protective (42). This may reflect a combination of incomplete efficacy, suboptimal adherence, and lack of universal access to HAART. In addition, long-term HAART may be complicated by direct nephrotoxicity or by metabolic disorders that are associated with the development of kidney disease, such as hypertension and diabetes (61,62). With the potential for a global epidemic of HIVAN, nephrologists must look beyond antiretroviral therapy for opportunities to have an impact on the epidemiology of HIV-related kidney disease. The nephrology community should support efforts to prevent the spread of HIV infection in susceptible minority populations, including educational campaigns, condom distribution, and harm reduction programs for injection drug users. After more than two decades of investigation into the pathogenesis of HIVAN, nephrologists should join the fight against the known causative agent: HIV itself. This should be done through political and social activism that supports better access to therapy, state and federally supported medical care for HIV-infected patients, and strategies to limit HIV transmission.

Disclosures
None.

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