Pathogenesis and Treatment of HIV-Associated Nephropathy

At the International AIDS Society–USA course in Atlanta in February, Paul E. Klotman, MD, summarized the characteristics of HIV-associated nephropathy and discussed recent findings that indicate a direct role of HIV in causing renal disease and that suggest that the kidney may be a viral reservoir.

HIV-associated nephropathy (HIVAN) has become the most common single diagnosis in HIV-infected patients with renal insufficiency. More than 90% of patients with HIVAN are black, with 50% having a history of injection drug use. Data from 1999 indicated that AIDS-associated end-stage renal disease (ESRD) was the third most common form of ESRD in blacks aged 20 to 64 years (after diabetes and hypertension), accounting for 8% of cases.

As a clinical syndrome, HIVAN is characterized by significant proteinuria and a rapid progression to ESRD. There is evidence, however, that potent antiretroviral therapy may slow the progression of the disease, and a greater number of patients with HIVAN are living longer following therapy. The disease has tended to occur in later-stage HIV infection, but cases of early onset have been seen and there is considerable interest in identifying renal changes that are associated with HIVAN early in the course of HIV infection. The disease is characterized by normal to enlarged kidneys on gross appearance and histopathologically by microcystic tubular disease with focal segmental glomerulosclerosis, frequently with glomerular collapse, and swelling of visceral epithelial cells on light microscopy.

No evidence of immune complexes is seen in the vast majority of cases. Biopsy in HIV-infected patients with proteinuria finds the typical features of HIVAN in about 60% of cases, and a variety of other disease entities are also found in association with factors such as hepatitis and drug use (Table 1).

Pathogenesis

A central question in the pathogenesis of HIVAN is whether the disease can be attributed to direct viral effects or to HIV-related changes in the cytokine milieu. Increasing evidence supports a direct role of HIV. Studies in a transgenic mouse model (Tg26), in which HIV-1 envelope and regulatory genes are expressed but gag and pol genes are deleted to render the virus noninfectious, have shown that renal disease in these animals closely resembles HIVAN; the resulting disease includes rapid progressive renal failure with the HIVAN features of microcystic changes and segmental sclerosis, including the collapsing variant. These findings that viral expression in the kidney is sufficient for the development of the disease suggest a direct role of HIV in its pathogenesis. Such findings, however, do not explain the strong predilection for disease in blacks.

To determine whether HIV is indeed present in the human kidney, Dr Klotman and colleagues have studied biopsy specimens from patients with HIVAN. Their research has involved using polymerase chain reaction (PCR) for long terminal repeat (LTR) circular forms of HIV (nonintegrated species that are thought to be degraded), which indicate recent nuclear import of the virus; in situ hybridization for messenger RNA (mRNA), which indicates ongoing viral transcription; and in situ DNA PCR to detect integrated proviral DNA.

Studies with PCR for LTR circular DNA showed the presence of this marker for recent cellular infection in approximately half of samples tested, including samples from patients with no detectable HIV in the peripheral blood (Figure 1A). Use of HIV-1 gag mRNA probes to determine whether such infection was occurring in renal cells (i.e., rather than in T cells or macrophages within the samples) found HIV-1 mRNA in the perinuclear region of renal tubular epithelial cells and glomerular cells, with clustering of positive cells apparently indicating efficient cell-to-cell transmission of the virus (Figure 1B). In situ PCR for HIV-1 DNA in these samples showed proviral infection of the nuclei of both tubular epithelial cells and podocytes in the glomerulus (Figure 1C).

Table 1. Diagnoses in HIV-Infected Patients with Proteinuria

- 60% have typical features of HIV-associated nephropathy on biopsy
  - Focal segmental glomerulosclerosis and microcystic tubulointerstitial disease
- Other common diagnoses
  - Focal segmental glomerulosclerosis alone (additional 10%-15%)
  - Membranoproliferative glomerulonephritis (10%)
  - Tubulointerstitial diseases (7%)
  - Minimal change disease (5%)
  - Membranous glomerulopathy (4%)
  - Lupus-like nephritis (3%)
  - Amyloidosis (3%)

Adapted from D’Agati and Appel, Semin Nephrol, 1998.
In subsequent studies, laser capture microscopy has been used to isolate renal epithelial cells shown to have integrated virus by in situ PCR to permit amplification of viral envelope V3 loop genetic sequences. These studies have found that the genetic variants of the virus in the kidney are distinct from the genetic variants in the peripheral blood of the same patient. This evolutionary divergence within patients suggests the presence of different selective pressures within the kidney.

The results of studies that have used markers for cell differentiation and proliferation suggest that viral infection in renal cells is associated with a loss of differentiation and an increased proliferation of podocytes and tubular epithelial cells. In summary, these studies have shown the presence of active viral replication in the renal cells of patients with HIVAN, and the finding of viral genetic material in samples from patients with no detectable HIV RNA in the peripheral blood at least suggests that the kidney could be a reservoir for HIV.

**Treatment**

No standard therapy for HIVAN has been developed, but there is evidence that potent antiretroviral therapy has a beneficial effect on disease progression. Angiotensin-converting enzyme inhibitors are sometimes used in patients with HIVAN, but their effects have not been evaluated in controlled studies. Steroids have also been reported to be of benefit in some cases, but the rationale for using them in a disease that is not immune complex-mediated is not clear.

The effects of potent antiretroviral therapy on HIVAN have yet to be examined in a controlled study. Protocols for investigating this are currently being reviewed by the AIDS Clinical Trials Group. In the absence of data from controlled trials, Dr Klotman’s group has generated a mathematical model for assessing the impact that potent therapy may have had on the increase in prevalence of ESRD in HIV-infected black patients. In brief, this model shows that the decrease in the prevalence of ESRD that can be attributed to HIVAN since 1995 can be explained by the introduction of potent antiretroviral therapy. The best fit of the existing data demonstrates that potent therapy has had an estimated 28% efficacy in reducing the increases in the number of HIV-infected black patients with ESRD. This model also predicts that, in the absence of drug treatment with 100% efficacy and with increases expected in the pool of patients at risk for developing HIVAN (i.e., black patients who are HIV-seropositive or living with AIDS), the size of the population of HIV-infected patients with ESRD will continue to increase.

Anecdotal evidence of a beneficial effect of potent antiretroviral therapy on very early onset HIVAN comes from the recent experience of Dr Klotman and colleagues in a patient who presented with ESRD during acute HIV seroconversion. Biopsy performed when the patient was about to undergo dialysis showed classic features of HIVAN, consisting of microcystic disease and focal segmental glomerulosclerosis. The patient was given aggres-

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**Figure 1.** Findings in renal biopsies in patients with HIV-associated nephropathy: (A) long terminal repeat circular DNA; (B) HIV messenger RNA; and (C) in situ polymerase chain reaction for HIV DNA. Adapted from Bruggeman et al, *J Am Soc Nephrol*, 2000.
The drug pressure was removed. Involvement of the microcystic changes that were present before potent antiretroviral therapy was initiated and resolution of collapsing glomerular disease with residual scarring. Collagen staining showed residual interstitial fibrosis, but it was markedly improved from the pretreatment condition. Assessing LTR circular viral DNA in biopsy samples found marked positivity before potent antiretroviral therapy, but not after. In addition, the resolution of renal failure after potent therapy was accompanied by a restoration of podocyte differentiation (as indicated by increased synaptopodin staining) and normalized cell proliferation (as indicated by normalized Ki67 marker positivity). In situ hybridization for viral mRNA, however, showed that some (low) level of viral transcription was ongoing.

Observations in this patient suggest both that renal damage due to active infection may be seen early in the course of HIV infection and that potent antiretroviral therapy may have a beneficial effect on the course of HIVAN by stopping such damage, thus making structural and functional reconstitution possible. In addition, the finding of ongoing viral transcription in the absence of active cellular infection during potent antiretroviral therapy supports the hypothesis that the kidney may be a viral reservoir; it remains unclear, however, whether the kidney might be a source of viral repopulation when the efficacy of potent antiretroviral therapy in suppressing viral replication is reduced or when drug pressure is removed.

### Suggested Reading


