

HIV-Associated Nephropathy: Epidemiology, Pathogenesis, and Treatment

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Initially described in 1984, human immunodeficiency virus-associated nephropathy (HIVAN) has now become a common disease within the HIV-seropositive population. It is a focal segmental glomerulosclerosis causing rapid deterioration of renal function. It is the most common cause of chronic renal disease in HIV patients and occurs almost exclusively in blacks. Through murine and human studies, it is now clear that HIVAN is caused by a direct effect of infection of renal cells by HIV-1 and that the virus actively replicates within renal cells. How the virus causes disease within cells is not yet understood, but there is evidence for factors within infected cells causing both proliferation and apoptosis. Steroids, angiotensin converting enzyme (ACE) inhibitors, and highly active antiretroviral therapy (HAART) have been used for the treatment of HIVAN, with HAART, in particular, showing a dramatic improvement in both the pathologic changes and clinical course of HIVAN.

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HUMAN IMMUNODEFICIENCY virus-associated nephropathy (HIVAN) was first described by Rao et al¹ in 1984 in 10 patients with acquired immune deficiency syndrome who developed a rapidly progressive renal disease. These patients had moderate to massive proteinuria and all developed end-stage renal disease within 16 weeks. Biopsy examinations revealed focal segmental glomerular nephritis. Six of the 11 patients had no known risk factors for renal disease, and the association was made between infection with HIV-1 and a characteristic nephropathy.

EPIDEMIOLOGY

Since its recognition as a unique disease entity, HIVAN has increased in incidence and is now the most common cause of chronic renal disease in HIV-seropositive patients. It is overwhelmingly a disease of blacks. Almost 90% of HIVAN cases occur in blacks. According to the United States Renal Data System (USRDS), HIVAN is the third leading cause of end-stage renal disease (ESRD) in blacks ages 20 to 64, behind diabetes mellitus and hypertension.² In an analysis of USRDS data, HIVAN as the cause of ESRD was associated strongly with black race; the only disease with a greater association was sickle cell anemia.³ This racial predilection has been confirmed in other countries as well, where in small biopsy studies

HIVAN was found to occur only in blacks.^{4,5} This has made HIVAN a disease of urban centers, with the greatest pool of patients coming from cities such as New York and Miami.⁶ Early data suggested that HIVAN was linked to intravenous drug use (IVDU), but it now seems clear that that apparent correlation is owing to the greater prevalence of IVDU in the black HIV population than in the white HIV population. In an autopsy study in Texas, 93% of the patients with HIVAN were black, and there was no significant difference in IVDU in those patients with HIVAN and those with other renal diseases.⁷ A retrospective review of HIV patients with renal disease in London found 7 of 17 had HIVAN; all were black, and none were IVDU patients.⁴ There is little data regarding the occurrence of HIVAN in Hispanics, but one retrospective study in a predominantly Hispanic HIV-positive patient population in the Bronx found a significantly higher prevalence of HIVAN in blacks than in Hispanics, with a comparative relative risk of 2.8-fold.⁸

CLINICAL CHARACTERISTICS

The classic pathologic lesion of HIVAN is focal segmental glomerulosclerosis with collapse of the glomerular tuft, associated with dilated tubules with microcysts (Fig 1). Tubuloreticular inclusions, once commonly observed by electron microscopy in as many as 25% of patients, has become a rare finding, possibly owing to more effective therapy⁹ (see the article on pathology by D'Agati et al for a further description). Clinically, HIVAN patients present with heavy proteinuria and hypoalbuminemia. HIVAN patients also typically are normotensive. This is a surprising finding considering the high incidence of hypertension in

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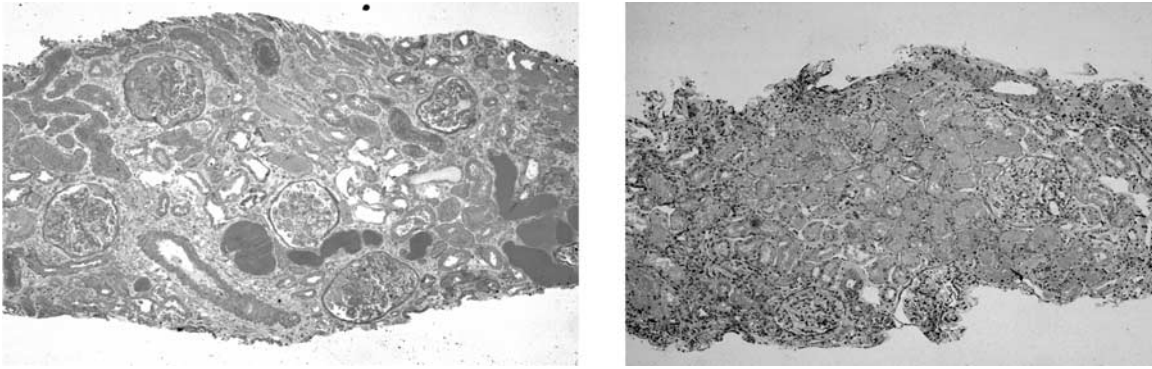


Fig 1. Renal biopsy with periodic acid-Schiff stain before and after HAART. A low-power view of a renal core biopsy specimen from a patient with HIVAN. The microcystic changes, proteinaceous casts, and focal glomerulosclerosis are evident before treatment with HAART. After 3 months of therapy, most of these changes have reversed or are in the process of resolving.

blacks. The absence of hypertension may be the result of a tubular defect in fluid and electrolyte handling. Ultrasound shows enlarged, echogenic kidneys. The degree of azotemia varies, but HIVAN always has been characterized by a rapid deterioration of renal function. In early studies of the natural history of HIVAN, time from diagnosis of HIVAN to initiation of hemodialysis was reportedly from weeks to months, with most patients dead within a year.¹⁰⁻¹² More recent data show that despite improved survival of HIV-seropositive patients in general, patients with ESRD secondary to HIVAN have higher mortality rates than those with ESRD of other causes. In a review of USRDS data from 1992 to 1997, 2-year survival was 36% for patients with HIVAN compared with 64% for all other patients with ESRD.³ HIVAN initially was believed to be a late manifestation of acquired immune deficiency syndrome because it appeared in patients with low CD4 counts and a history of opportunistic infections.¹³ There are now reported cases, however, of HIVAN developing in patients at the time of seroconversion, indicating that it also may present early in the course of HIV.^{14,15} Small studies have produced conflicting data regarding the relationship of HIV viremia to the presence of HIVAN.^{16,17}

PATHOGENESIS

Murine Models of HIVAN

The direct role of HIV-1 in the nephropathy seen in individuals infected with HIV has been the subject of considerable controversy given the mul-

titude of possible confounding factors. Theories of etiologic factors in HIVAN have included opportunistic infection, medication, IVDU, as well as indirect and direct effects of the virus itself.

Murine models have established the direct role of expression of HIV-1 genes as sufficient for the development of HIVAN. Several transgenic mouse models that express replication-defective HIV proviral constructs develop a renal disease with clinical and pathologic similarities to HIVAN in humans.¹⁸⁻²⁰ Rat transgenics have been described recently that also develop renal disease.²¹ Transgenic mice were mated with nude mice, producing progeny whose cells expressed HIV-1 but who lacked mature T cells. These progeny developed HIVAN, showing that the disease requires HIV-1 expression but does not depend on T-cell mediated mechanisms.²² Bruggeman et al²³ performed a reciprocal renal transplant between HIV transgenic mice and normal mice. The normal mice with transgenic kidneys developed HIVAN, whereas the transgenic mice with normal kidneys had neither proteinuria nor histopathologic changes at the time of their death. These studies provide evidence not only that HIV-1 must be present, but it must be present in renal cells for HIVAN to occur in this model.

In Vitro Evidence for Renal Cell Infection

In vitro data for HIV-1 infection of human renal cells has been conflicting. Green et al²⁴ and Tokizawa et al²⁵ found a low level of infection in mesangial cells, but Alpers et al²⁶ were unable to

produce mesangial cell infection despite attempts using multiple cloned HIV-1 strains. Ray et al²⁷ were able to infect tubular epithelial cells collected from the urine of seropositive children, but only in the presence of very high viral titers. Conaldi et al²⁸ showed a productive infection of tubular epithelial cells by the presence not only of proviral DNA and viral RNA in cells, but the release of viral progeny in culture. Despite these studies indicating permissiveness of renal cells to HIV-1 infection in vitro, the high level of viral titers required and the low level of viral products detected have made the in vivo significance uncertain.

In Vivo Evidence for Renal Cell Infection

In 1989, Cohen et al²⁹ were the first to show HIV-1 in glomerular and tubular epithelial cells in human renal biopsy samples. Subsequent investigators were unable to confirm these findings.^{27,30,31} Eventually, Kimmel et al^{32,33} found HIV-1 DNA and antigen in microdissected renal biopsy tissue, but it was impossible to exclude contamination by infiltrating leukocytes.

Recently, Bruggeman et al³⁴ showed that renal cells were infected by HIV-1. In renal biopsy tissue of seropositive patients with and without renal disease, viral messenger RNA (mRNA) was detected in 14 of 20 of those with renal disease, and was found most frequently in tubular epithelial cells. In the samples containing tubules expressing HIV mRNA, surrounding tubules often were negative for viral mRNA, indicating a focal infection. These findings were confirmed by the presence of viral DNA in nuclei of glomerular and tubular epithelial cells. Presence of circularized DNA, a marker of recent infection and active replication, was also seen in 16 of the 23 seropositive subjects. Furthermore, viral DNA, mRNA, and circularized DNA were detected in kidney tissue even in subjects without detectable serum viral loads.³⁴

Marras et al³⁵ provided further evidence for infection and viral replication within renal cells. Renal epithelial cells from biopsy samples of 2 patients with HIVAN were captured by using laser microdissection to exclude contamination by infiltrating leukocytes. HIV-1 DNA and mRNA were detected in cells, and polymerase chain reaction was performed on DNA extracted from these cells as well as on DNA from peripheral blood mononuclear cells. Phylogenetic analysis of amplified

envelope sequences revealed that renal cell isolates formed subclusters but were divergent, suggesting complete cycles of viral replication. In addition, the envelope sequences formed clusters that were distinct significantly from the sequences from peripheral blood mononuclear cells, suggesting compartmentalization.³⁵

These studies show that renal epithelial cells are permissive to infection by HIV-1 in vivo and that the virus is replicating actively within these cells. They further suggest that the kidney may serve as a reservoir for HIV-1. Viral reservoirs are an important and possibly major source of the re-emergence of viremia when HIV therapy is discontinued.³⁶ Thus, this is an additional reservoir that will need to be addressed in the future as therapeutic strategies are developed.

MECHANISMS OF INFECTION

CD4-mediated entry of HIV-1 into T cells and macrophages has been shown to require a G protein-coupled coreceptor that permits envelope fusion and viral entry. The most commonly isolated strains of virus have used CCR5 and CXCR4 or both, though several other chemokine and orphan receptors have been found to permit infection by a small number of HIV-1 strains in vitro. The importance of second-receptor molecules is shown in those individuals with a deletion mutation in the CCR5 gene. $\Delta 32$ CCR5 homozygotes are highly resistant to HIV-1 infection and infected heterozygotes have a slower progression to disease.³⁷ Second receptors determine cell tropism and influence viral pathogenesis. No study to date, however, has shown direct evidence that any given coreceptor functions in entry of HIV-1 into renal cells.

MECHANISMS OF DISEASE

Proliferation

Renal biopsy examinations of patients with HIVAN have shown both proliferative and apoptotic changes. The primary process is uncertain, but because HIVAN kidneys are enlarged, proliferation is most likely the predominant process.

Transforming growth factor- β (TGF- β) is a fibrogenic cytokine that regulates human immune function and has been shown to regulate HIV replication.³⁸ A study of human kidneys found increased deposition of matrix proteins and increased levels of TGF- β in those kidneys with HIVAN

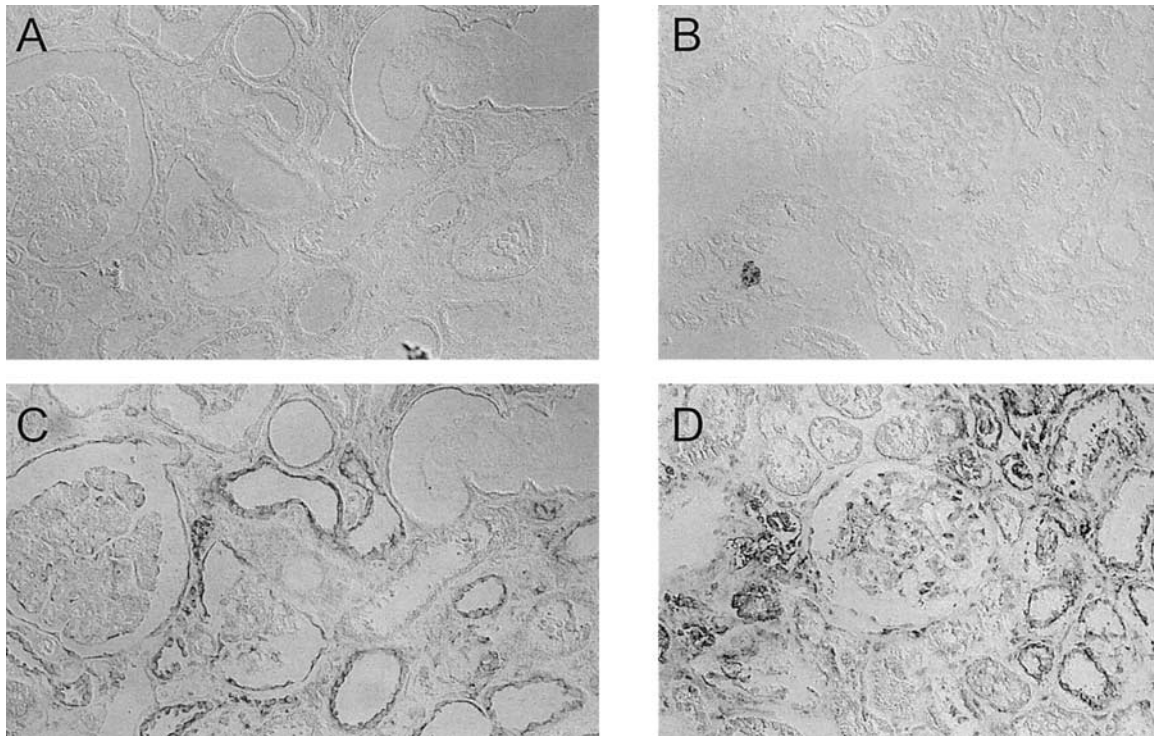


Fig 2. HIV-1 mRNA detected by in situ hybridization in kidney biopsy specimens obtained before and after the initiation of HAART (50 \times). The use of an antisense probe generated from the gag region shows the presence of HIV-1 RNA in tubular cells and podocytes as well as interstitial inflammatory cells (C) before and (D) after the initiation of HAART. A control sense probe showed no staining of the (A) pretreatment biopsy specimen, and (B) hybridization of renal tissue from an HIV-1-negative patient with systemic lupus erythematosus using the antisense probe also showed no staining. (Reprinted with permission from Winston et al:¹⁵ Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med* 344:1979-1984, 2001. Copyright © 2001 Massachusetts Medical Society. All rights reserved.)

compared with normal kidneys and with kidneys with thin basement membrane and minimal change nephropathies. This was true even when compared with kidneys of HIV-infected individuals without HIVAN.³⁹

Basic fibroblast growth factor (bFGF) has been linked to renal epithelial cell proliferation in some disease states. In a study comparing HIV transgenic mice with normal mice, transgenic kidneys had increased bFGF and a greater number of bFGF binding sites. Transgenic tubular epithelial cells were found to express bFGF and transgenic epithelial cells or nontransgenic cells treated with bFGF exhibited an increased rate of proliferation compared with controls.⁴⁰

Renal mesangial cell cultures incubated in sera collected from HIV-seropositive patients showed a greater degree of proliferation than those cells incubated in normal control sera. This effect was

concentration dependent, and was inhibited in the presence of azidothymidine (AZT).⁴¹

Renal epithelial cells of transgenic mice⁴² and biopsy specimens from a human subject with HIVAN¹⁵ showed an increased expression of markers of proliferation such as the Ki-67 antigen, and a decreased expression of markers of differentiation such as synaptopodin. HAART treatment of a patient with HIVAN abolished evidence of viral replication in kidney (Fig 2) and reversed these phenotypic changes (Fig 3).¹⁵

Apoptosis

In vitro, renal tubular epithelial cells undergo rapid cell death and apoptosis after infection with HIV-1.²⁸ In this study, HIV-1 infection caused an up-regulation of Fas, a tumor necrosis factor receptor. The degree of apoptosis was unchanged by the presence of anti-Fas antibody, but was even

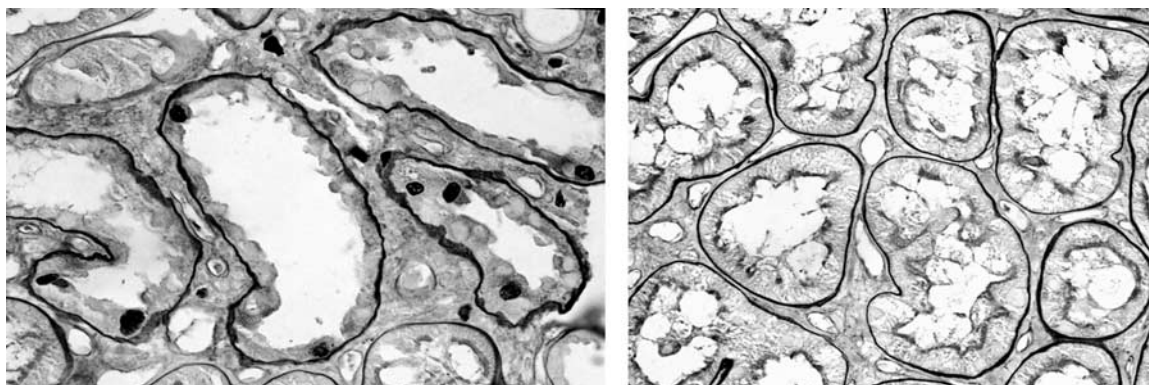


Fig 3. Ki-67 antigen expression in a patient with HIV-associated nephropathy before and after HAART. (Reprinted with permission from Winston et al:¹⁵ Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med* 344:1979-1984, 2001. Copyright © 2001 Massachusetts Medical Society. All rights reserved.)

greater in the presence of an agonistic antibody to Fas. Apoptotic changes seen in infected cells were not seen in epithelial cells treated at the time of infection with an inhibitory antibody to caspase, a proteolytic enzyme associated with programmed cell death. Viral replication in these cells continued unchanged.

In a study by Singhal et al,⁴³ human glomerular epithelial cells exhibited a concentration-dependent pathologic response to treatment with HIV-1 gp120 envelope protein. Cultures treated with low concentrations of gp120 showed increased cellular proliferation and increased proliferating nuclear cell antigen, indicating enhanced mitogenesis. These changes were inhibited by antibodies to protein kinase C and to tyrosine kinase. Cultures treated with high concentrations of gp120 showed an increased number of apoptotic and necrotic cells and a greater degree of DNA fragmentation. The effects of low and high concentrations of gp120 were inhibited by the addition of anti-gp120 antibodies.⁴³ These data suggest a direct role specifically for gp120, perhaps through signaling pathways.

Although these studies offer insights into viral and renal host events in HIV infection and possibly in HIVAN, the relative importance of each of these in the progression to disease is uncertain.

DIFFERENCES IN HOST FACTORS

Although most transgenic mice develop HIVAN, some do not despite the same level of HIV transgene expression. In the study by Brugge-

man et al,³⁴ of the 7 seropositive subjects without HIVAN (2 without renal disease and 5 with other forms of renal disease), 6 were found to have renal cell infection by the presence of viral mRNA, DNA, or both. These findings suggest that not all patients with renal infection develop HIVAN. Therefore, host factors must confer a vulnerability to HIVAN, and the data suggest that the vulnerability must lie in downstream events once infection is established. The occurrence of HIVAN almost exclusively in blacks suggests that there is a race-associated genetic difference in response to renal infection with HIV-1. Genetic polymorphisms in these susceptibility loci likely confer a risk for kidney disease in general. One small study found that patients with HIVAN had a significantly greater number of close relatives with end-stage renal disease than did seropositive patients without renal disease.⁴⁴ It also is possible that the genetic difference impacts specifically on host response to renal cell infection. Unfortunately, too little is understood regarding the mechanisms of pathogenesis to allow more than speculation at this time. Clarification of these mechanisms and the host factors that modify them will provide opportunities for future treatments and even prevention of HIVAN, and possibly insight into selected forms of renal disease.

TREATMENT

Corticosteroids

Steroids have long been used to combat effects of inflammatory processes and have been used

successfully in the treatment of classic idiopathic FSGS. The presence of infiltrating leukocytes and increased levels of TGF- β in HIVAN kidneys provides evidence for a role for inflammation in the progression of HIVAN.

In a 1994 report, Smith et al⁴⁵ prospectively followed-up 4 consecutive patients with biopsy examination-proven HIVAN treated with prednisone 60 mg/d. All 4 had dramatic short-term improvement in creatinine levels after a short course of prednisone, though urine protein level essentially was unchanged. However, 2 of the patients developed opportunistic infections that required a rapid taper of steroids. A case report by Briggs et al⁴⁶ describes a man presenting with the clinical syndrome of HIVAN that was confirmed by a biopsy examination showing collapsing focal segmental glomerulosclerosis, epithelial cell injury, tubulointerstitial infiltrates, as well as a thrombotic angiopathy. The patient's creatinine level decreased from a peak of 7.5 to 3.9 after 6 weeks of prednisone treatment, and after 9 weeks the proteinuria level decreased from 15.7 g/d to 6.1 g/day. More dramatically, a repeat biopsy examination at 9 weeks showed a resolution of the thrombotic microangiopathy, a reduction in the tubulointerstitial inflammation and injury, and no progression of the glomerulosclerosis. Watterson et al⁴⁷ report a patient with HIVAN on maintenance hemodialysis who was treated with prednisone for cardiomyopathy, whose renal function improved enough after 6 weeks to allow discontinuation of dialysis. His renal function was stable for 4 months, at which time azotemia worsened and he again responded to prednisone. A prospective observational study followed-up 20 patients with HIVAN for a median of 44 weeks on prednisone. Seventeen had a decrease in creatinine level, and 12 had a decrease in the degree of proteinuria. Serious new opportunistic infections developed in 6 patients.⁴⁸ A recent retrospective cohort study of 21 HIVAN patients compared 13 who received steroid treatment with 8 who did not. At 3 months, none of the 13 patients receiving prednisone had progressed to ESRD, whereas 5 of the 8 in the cohort group were on dialysis. At 12 months, however, 8 of the patients in the treatment group were dead or on dialysis (with 2 lost to follow-up), compared with 7 patients in the cohort group (with 1 patient lost to follow-up). There was no difference in incidence of serious infections

between the 2 groups when adjusted for the difference in duration of follow-up evaluation, though there was an increased number of days in-hospital in the steroid-treated group.⁴⁹

These studies showing improvement in response to prednisone are limited by their reliance on observational and retrospective data, making them vulnerable to confounding variables. The patient described by Watterson et al⁴⁷ was started on AZT shortly before beginning prednisone treatment. Further, despite short-term clinical and even pathologic improvements, the patient's long-term prognosis remained poor. For example, in the study by Smith et al,⁴⁸ the median time to death, ESRD, or last follow-up in patients receiving steroids was 32 weeks. The data are conflicting regarding increased risk for opportunistic infections. Last, no study to date has shown an improvement of HIVAN in pediatric patients on steroids.⁵⁰⁻⁵²

ACE Inhibitors

ACE inhibitors have been shown to reduce proteinuria and progression of renal disease in patients with diabetic and nondiabetic renal disease. Proposed mechanisms are reduction in glomerular hydrostatic pressure, decreasing permeability to proteins of the basement membrane, and decreasing angiotensin II-stimulated production of cytokines including TGF- β . Given the increased expression of TGF- β in HIVAN kidneys and the finding of increased serum ACE levels in HIV-seropositive patients,⁵³ ACE inhibitors might be expected to show improvement in HIVAN.

In 1994, Burns et al⁵⁴ described a patient with biopsy examination-proven HIVAN treated with fosinopril. After 14 days of treatment, the 24-hour urine protein level decreased from 6.6 to 3.2 g. Fourteen days after fosinopril was discontinued, urine protein level increased to 5.2 g/24 hours. A prospective cohort study of HIVAN patients by Kimmel et al⁵⁵ compared 9 patients receiving captopril with 9 patients not treated with any ACE inhibitors. Renal failure progressed to ESRD in all of the control patients and 7 of the 8 surviving captopril patients, but time to dialysis was 37 ± 5 days in the control group compared with 156 ± 71 days in the captopril group. However, use of anti-retrovirals also was found to be associated with a significant improvement in renal survival in this study. Another cohort study by Burns et al⁵⁶ followed-up 20 HIVAN patients, 12 of whom ac-

cepted fosinopril therapy and 8 of whom refused. Those patients taking fosinopril had significantly lower levels of creatinine and proteinuria at the end of 12 or 24 weeks than those who refused. In the subgroup of patients who were nephrotic at baseline, the 4 who refused treatment were all on hemodialysis by 16 weeks, whereas none of the 5 fosinopril patients were on dialysis. A study by Bird et al⁵⁷ investigated the clinical and pathologic effects of captopril versus vehicle treatment in transgenic mice with HIVAN and wild-type mice. Transgenic mice receiving vehicle had higher urine protein and serum creatinine levels when compared with transgenic mice receiving captopril or another control group of wild-type mice. Untreated transgenic mice also had a greater degree of glomerular and corticotubulointerstitial injury than the other groups. HIV transgene expression was the same in both the vehicle- and captopril-treated transgenic mice. Similarly, presence of TGF- β and TGF- β mRNA was the same in both groups. This indicated that captopril appears to ameliorate some of the deleterious effects of HIV expression in kidney.

Though the murine data is suggestive, studies in humans are observational and nonrandomized. In addition, none of the studies controlled for the effects of ACE inhibition on blood pressure. Furthermore, viral burden or treatment efficacy were not considered or addressed.

Antiretrovirals

The first case report of antiretroviral therapy for HIVAN was in 1989, when a HIVAN patient started on AZT had remission of his nephrotic syndrome and renal survival for 11 months before relapse.⁵⁸ This was in striking contrast to the typical renal survival in HIVAN at that time of weeks to months, and corresponded to the mean duration of remission of other manifestations of acquired immune deficiency syndrome on lone AZT therapy. Further reports supported these findings.^{59,60}

Highly active antiretroviral therapy (HAART), consisting of a triple-drug regimen, was initiated in HIV-seropositive patients in 1997 and is now the standard of care in progressing patients. In 1998, Wali et al⁶¹ reported a patient who, after 13 weeks of HAART, showed a decrease in serum creatinine and urine protein levels and a recovery or improvement in glomerular and interstitial damage. In Winston et al's¹⁵ description of a patient fol-

lowed-up on HAART therapy, serum creatinine and urine protein levels decreased dramatically after 6 weeks of treatment. A renal biopsy procedure performed after 3 months of treatment revealed an improvement of glomerulosclerosis, tubulointerstitial disease, and resolution of changes on electron microscopy. The degree of renal epithelial HIV mRNA expression was unchanged, despite a viral load reduced to undetectable levels. No circularized HIV-1 DNA was found after HAART therapy, showing inhibition of new renal infection.¹⁵ Recent data also suggest improved survival of HIVAN patients on dialysis who are receiving HAART. A retrospective chart review of 22 HIVAN patients found a mean survival of 28 ± 17 months in those patients on HAART and a mean survival of 13 ± 10 months in those patients on 2 or fewer antiretrovirals.⁶²

Because HAART is now the standard of care for progressing patients, it is difficult to study its effects on HIVAN in a controlled fashion. Schwartz et al developed a mathematical model using available epidemiologic data on HIV-infected patients in the ESRD database² and Centers for Disease Control data for HIV-seropositive patients. This model suggests that HAART reduces the incidence of ESRD in HIVAN and the mortality of HIV, with an overall efficacy of 23% (Elissa Schwartz, personal communication).

Because HIVAN is a result of direct infection of renal cells, HAART would appear to be a rational and necessary means of treatment for HIVAN. Epidemiologic data support this hypothesis. Steroids and ACE inhibitors may have a role in treatment, but it is almost certainly as an adjunct by modifying downstream effects of HIV infection in the kidney.

SUMMARY

Our understanding of the pathogenesis of HIVAN has improved greatly and, as a result, more rational strategies for therapy are emerging. Over the past 5 years, it has become clear that HIVAN is caused by a direct effect of infection of renal cells by HIV-1 and that the virus actively replicates within renal cells. How the virus causes disease within cells is not yet understood, but there is evidence for factors within infected cells causing both proliferation and apoptosis. Future studies are needed to address mechanisms of viral entry, the genetic differences that predispose blacks to

HIVAN, and the host responses to HIV expression that induce disease.

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