Pathogenesis and Treatment of HIV-Associated Renal Diseases: Lessons from Clinical and Animal Studies, Molecular Pathologic Correlations, and Genetic Investigations

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HIV infection is associated with several renal syndromes, including acute renal failure. Chronic renal failure directly linked to HIV infection includes thrombotic microangiopathic renal diseases, immune-mediated glomerulonephritides, and HIV-associated nephropathy. A renal biopsy may be necessary for diagnosis. The development of HIV-associated nephropathy has been definitively linked to renal cellular infection, but the disease affects only a minority of patients, typically men of African descent. Therefore, factors determining disease expression in infected patients must now be emphasized.

The pathogenic mechanisms involved in HIV-associated renal disease remain obscure. Genetic factors, as well as renal cellular responses, mediated by HIV proteins (including an immune-activated microenvironment) capable of presenting antigen in susceptible hosts probably explain most cases. HIV-associated nephropathy has a characteristic pathologic phenotype, including glomerular, tubular, and interstitial changes, and ultrastructural findings. Infection of the glomerular epithelial cell, or podocyte, and consequent structural and biochemical changes may be pivotal in pathogenesis. The HIV-1 transgenic mouse is an important model for understanding disease pathogenesis, particularly the role of HIV proteins in mediating renal tissue injury.

Rigorously controlled randomized trials have not evaluated treatment, but corticosteroids and angiotensin-converting enzyme inhibitors have been used. Highly active antiretroviral therapy seems to have decreased the incidence of end-stage renal disease related to HIV infection and, in case reports, to have improved renal functional and pathologic outcomes of HIV-associated nephropathy. Outcomes in patients undergoing hemodialysis and peritoneal dialysis have improved, and current research focuses on renal transplantation for treatment of HIV-infected patients.

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dialysis population (26). The prevalence of renal disease related to HIV infection has stabilized or are decreasing (25–27) (Figure 1). Between 1995 and 1999, the number of new HIV-infected patients in the dialysis program was low but had tripled from 1985 to 1988 (25, 27) (Figure 1). However, subsets of the population, such as young black men, were at particularly high risk for developing nephropathy (28, 29). The relative risk for end-stage renal disease from AIDS or an AIDS-defining diagnosis from 1995 to 1999 is 0.39 for women compared with men (Eggers PW. Personal communication). Risk between men and women does not vary by race or ethnicity, but black patients had a relative risk of 51.1 for developing nephropathy (28, 29).

Chronic Renal Disease: End-Stage Renal Disease

Currently, HIV-infected patients make up approximately 1% to 2% of the population with end-stage renal disease (25–27) (Figure 1). The incidence geographically reflects the national distribution of AIDS and HIV infection (25, 26). The prevalence of HIV infection in the dialysis program is probably higher because of confidentiality issues and the lack of biopsies in most patients. During the late 1980s, the number of HIV-infected patients in the dialysis program was low but had tripled from 1985 to 1988 (25, 27) (Figure 1). However, subsets of the population, such as young black men, were at particularly high risk for developing nephropathy (28, 29). The relative risk for end-stage renal disease from AIDS or an AIDS-defining diagnosis from 1995 to 1999 is 0.39 for women compared with men (Eggers PW. Personal communication). Risk between men and women does not vary by race or ethnicity, but black patients had a relative risk of 51.1 for developing end-stage renal disease from AIDS or an AIDS-defining diagnosis compared with white patients. Although early work suggested a rapidly increasing number of HIV-infected patients (28), the number and proportion of patients undergoing dialysis who had renal disease attributed to HIV infection have stabilized or are decreasing (25–27) (Figure 1). Between 1995 and 1999, the number of new patients with HIV infection in the U.S. hemodialysis program ranged from 1131 to 1187 and did not rise proportionately with the increase in HIV infection or the U.S. dialysis population (26).

Chronic Renal Failure

The prevalence of renal disease related to HIV infection is unknown, rendering epidemiologic assessments problematic (29). The designation of chronic kidney disease in HIV-infected patients depends on the screening techniques used (30). Data before (30, 31) and after (32) the introduction of highly active antiretroviral therapy suggest a prevalence of abnormal proteinuria of about one third, using various criteria. A European autopsy study of HIV-infected patients, most of whom had developed AIDS, showed proteinuria in 18%, nephropathy in 36%, and renal pathology in 43% (31). Less than 10% of a cohort of HIV-infected women had proteinuria or renal insufficiency at baseline, but 14% developed kidney disease during a mean 21-month follow-up (33). In a large study of HIV-infected women, viral load and stage of infection were associated with proteinuria and progressive nephropathy but presence and type of antiretroviral therapy were not (32).

Three types of chronic kidney disease are directly caused by HIV infection: HIV-associated thrombotic microangiopathies, HIV immune-mediated renal diseases, and classic HIV-associated nephropathy (4, 27). Because of improved understanding of the HIV life cycle, advances in molecular biological tissue evaluation, and the development of relevant animal models, stronger pathogenic inferences can be made about HIV-associated nephropathies compared with other renal diseases. Elucidating the pathogenesis of HIV-associated renal diseases also permits better understanding of pathogenic mechanisms underlying more common renal diseases.

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

The thrombotic microangiopathies, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, are thought to occur because of endothelial cell dysfunction partially mediated by HIV proteins (4, 15, 34–36). Renal cellular apoptosis (4, 15, 34, 37), as well as inhibition of von Willebrand factor–cleaving protease (38), may play key pathogenic roles. The disease spectrum is characterized by a pentad of findings with variable expression: fever, neurologic dysfunction, thrombocytopenia, microangiopathic hemolytic anemia, and renal insufficiency with hematuria. High-level proteinuria is uncommon, which helps differentiate these syndromes from immune-mediated diseases and HIV-associated nephropathy (4). However, nephrotic-range proteinuria does occur (39–41), perhaps because of the coexistence of two diseases (41). Although spontaneous remissions occur (40), the renal disease often resists treatment. Treatment with glucocorticoids (41, 42), plasma and immunoglobulin infusions, plasmapheresis, antiplatelet drugs, vincristine, and splenectomy has variable

Figure 1. Percentage of HIV-infected patients receiving hemodialysis in the U.S. hemodialysis program.

success (15, 27), but lack of controlled trials precludes evidence-based recommendations.

**HIV-ASSOCIATED IMMUNE-MEDIATED GLOMERULONEPHRITIDES**

Autopsy and biopsy series in HIV-infected patients with renal disease have established a prevalence of proliferative glomerulonephritis of 10% to 80% (42–49). Immune complex glomerulonephritis associated with HIV infection has several different histologic presentations (43, 49), including proliferative, lupus-like, and mixed proliferative or sclerotic forms (43). Other types of glomerulonephritis, such as membranoproliferative glomerulonephritis, membranous nephropathy, fibrillary and immunotactoid glomerulonephritis, and postinfectious glomerulonephritis, also occur in HIV-infected patients (43, 45, 46, 49–52). The renal disease, however, may not be intimately associated with HIV infection. Rather, it may be a consequence of coexistent infection, such as renal disease related to hepatitis C or B (49, 53–55), a response to infection in patients with disordered humoral immunity (49, 56), or a coincidental finding (49). A renal biopsy with immunohistochemical and molecular biological analyses is necessary to make a precise etiologic diagnosis, but this is usually not possible in clinical practice. By using classic research techniques, we showed that the immune response to HIV infection could culminate in specific HIV immune-mediated glomerulonephritis (57).

IgA nephropathy occurs in HIV-infected patients (4, 49, 58, 59). Its incidence and prevalence are unknown. In an autopsy study, 7.75% of persons with AIDS had diffuse mesangial IgA deposits (60). IgA nephropathy in HIV infection seems to be relatively common in men of European descent but uncommon in people of African descent (27, 49, 60), as in uninfected populations (61). We showed that IgA nephropathy in two patients was the result of an autoimmune reaction to HIV peptides (59). HIV-associated IgA nephropathy is generally indolent, characterized by proteinuria, hematuria, and mild renal insufficiency.

European and Asian case series of patients with HIV infection and renal disease who underwent biopsies or autopsies show that patients of European descent typically have glomerulonephritis, while patients of African descent in the same centers usually have HIV-associated nephropathy (31, 43, 45–49). These disparities and the clustering of renal disease in families of patients with HIV infection and end-stage renal disease (62) suggest a genetic component for developing both HIV-associated immune-mediated renal diseases and HIV-associated nephropathy.

Remarkable responses have been reported in patients with immune-mediated renal diseases treated with angiotensin-converting enzyme (ACE) inhibitors, glucocorticoids, or antiretroviral therapy (51, 63–65), but properly designed randomized, controlled trials have not assessed such therapies.

**CLASSIC HIV-ASSOCIATED NEPHROPATHY**

Although some researchers suggest that HIV-associated nephropathy comprises a spectrum of mesangial diseases and matrix production disorders (66), variants of focal segmental glomerulosclerosis, including collapsing glomerulopathy, were reported in most HIV-infected patients with renal disease who underwent renal biopsy (4, 27, 67, 68). HIV-associated nephropathy is characterized by large, echogenic kidneys on ultrasonography, nephrotic-range proteinuria, and renal insufficiency. Although it has been argued that HIV-associated nephropathy is a late complication (67, 69), it can clearly occur at any stage of HIV infection and is occasionally the presenting manifestation of infection (70–72). The pathologic findings are pathognomonic (66–68, 73, 74). Although clinical findings are suggestive, a biopsy is necessary for diagnosis. Before the introduction of highly active antiretroviral therapy in 1996, HIV-associated nephropathy was typified by an extremely rapid progression that was thought to be inexorable.

**Pathogenic Considerations**

The pathogenesis of HIV-associated nephropathy is unknown, but three lines of evidence definitively link the disease to viral infection: 1) the finding of HIV-associated nephropathy in infected infants of HIV-infected mothers (75); 2) the reproduction of the disease in HIV-1 transgenic mice, rats, and simian models of retroviral infection (15, 76–79); and 3) reports of reversal of renal histologic and laboratory abnormalities in a small set of patients with biopsy-proven HIV-associated nephropathy after highly active antiretroviral therapy (70, 72).

We showed the ubiquitous presence of HIV DNA in renal tissue of HIV-infected patients (44), but only recently has human renal viral infection been demonstrated by the localization of HIV-1 messenger RNA in renal tissue, specifically glomerular and tubular epithelial cells (72, 80–82). However, proteinuria is present in less than half of HIV-infected patients (30–33), and advanced stages of chronic kidney disease are an uncommon complication of HIV infection (4, 27, 66, 67). Therefore, factors other than simple infection of renal cells or the infiltration of infected immune cells in renal tissue probably mediate the expression of nephropathy (4, 44). Large-scale clinical epidemiologic and pathologic studies of the relationship of renal HIV infection to the expression of disease, with the proper positive and negative controls, remain to be performed.

Cytokines and growth factors, produced by infiltrating immune or renal cells, undoubtedly play roles in mediating disease pathogenesis in susceptible hosts through effects on renal cells or the viral life cycle. The presence of an immune cell infiltrate in the renal tissue of patients with HIV-associated nephropathy remains unexplained, but clinicopathologic data implicate the macrophage in the pathogenesis of HIV-associated nephropathy (83). Chemo-
Figure 2. Interferon-α protein expression in renal tissue compartments.

Interferon-α protein was assessed in microdissected renal glomerular and interstitial tissue from 6 patients with HIV-associated nephropathy, 4 patients with HIV-associated immune-mediated glomerulonephritis, 3 HIV-infected patients who died without autopsy evidence of renal disease, 9 patients with idiopathic focal segmental glomerulosclerosis in the absence of HIV infection, and renal tissue of uninfected patients without clinical or pathologic evidence of renal disease by high-performance immunoaffinity chromatography and chemiluminescent enzyme-linked immunosorbent assay. Renal interstitial and glomerular interferon-α protein levels were significantly higher in renal tissue from patients with HIV-associated nephropathy than in tissue from all other groups ($P = 0.002$; analysis of variance). A similar pattern was noted for nonpolymorphic major histocompatibility II locus and interferon-γ receptor protein levels. Error bars indicate SEs. *$P = 0.002$. 

Kines mediate infiltration of tissue by monocytes, macrophages, lymphocytes, neutrophils, and eosinophils and have been implicated in nephropathogenesis (84). Certain chemokine receptors function as second receptors for the engagement of HIV virions and the cell membrane (85). Mutations in chemokine receptor proteins are associated with resistance to HIV infection and improved prognosis (86). Chemokine receptor RNA has been detected in renal tissue (84, 87, 88), but detecting chemokine receptors in HIV-associated nephropathy tissue is limited to infiltrating immune cells (89). We investigated the relationship of tissue transforming growth factor-β (90) and chemokines (91) to the presence of nephropathy by comparing biopsy specimens from patients with HIV-associated nephropathy, HIV-associated glomerulonephritis, and idiopathic focal glomerulosclerosis without HIV infection, with appropriate controls. Chemokine levels were increased in renal tissue from patients with HIV infection regardless of the presence of renal disease (91). This finding suggests that chemokines might help prevent productive infection of renal cells by interacting with renal chemokine receptors, thereby decreasing the number of renal cells infected and the subsequent expression of nephropathy. Tissue proteins associated with antigen presentation and response to infection, including MHC class II proteins, interferon-α, and interferon-γ receptor protein, were specifically associated with HIV-associated nephropathy, suggesting that genetic susceptibility, the host response, and a microenvironment characterized by immune activation are critical to nephropathogenesis (Figure 2). The finding of high levels of interferon-α is consistent with the pathologic feature of tubuloreticular inclusions (4, 68, 73, 74, 91). Human (92) and animal (93) studies suggest that apoptosis, perhaps mediated by HIV proteins, plays an important role in nephropathogenesis. A complex interrelationship probably exists among renal infection, effects on renal cell matrix biology, cytokine, growth factor, and chemokine responses, mediated by host factors (including genetic susceptibility and socioeconomic status) leading to the development of HIV-associated nephropathy.
TREATMENT OF HIV-ASSOCIATED NEPHROPATHY

No rigorously controlled randomized trials have evaluated treatment of HIV-associated nephropathy (27, 94). Glucocorticoid therapy produced impressive decreases in urinary protein excretion and improved renal function (95), but treatment before the introduction of highly active antiretroviral therapy was associated with a high prevalence of serious complications (94–97). More recent studies suggest that steroid treatment is associated with improved renal functional outcomes and less morbidity, perhaps secondary to concomitant highly active antiretroviral therapy (96–98). Two studies completed before the introduction of highly active antiretroviral therapies suggest that ACE inhibitors have clinically significant effects on renal survival (99, 100). This effect was confirmed in the HIV-1 transgenic mouse (101). The mechanism of action of these drugs is unknown. Steroids may decrease the associated component of interstitial inflammation (41, 94), while ACE inhibitors may affect interstitial immune cellular function and the generation of tissue cytokines (4, 94, 99).

Antiretroviral drug therapy has been associated with beneficial effects on renal functional status, morbidity, and mortality (4, 27, 94, 102–104). In patients treated with captopril, use of antiretrovirals was independently associated with improved renal survival (99). Two dramatic case reports suggest that treating patients with HIV-associated nephropathy with highly active antiretroviral therapy may result in remission of both renal pathologic and functional abnormalities (70, 72), although the kidney may remain a reservoir of infection (72, 81, 82). Outcomes of HIV-infected patients treated with hemodialysis and peritoneal dialysis have improved and the incidence of HIV infection in the dialysis program seems to have decreased concomitantly with the introduction in 1996 of highly active antiretroviral therapy (25–27, 105, 106) (Figure 1). Although the immunosuppression of HIV-infected patients is a concern, the prospect of transplantation for carefully selected HIV-infected patients is exciting but controversial (27, 107–111). Some of the immunosuppressive medications used in clinical transplantation may have antiretroviral effects (27, 109). Successful transplantation in HIV-infected patients who have received highly active antiretroviral therapy and have undetectable viral loads has been reported in abstract form, and a multicenter study is in progress (27, 108). Murphy and colleagues transplanted kidneys in 23 patients who were receiving antiretroviral therapy, had CD4 cell counts greater than 0.200 × 10⁹ cells/L, and had undetectable viral loads; the graft survival rate was 87% (27, 108).

APPROACH TO THE HIV-INFECTED PATIENT WITH CHRONIC KIDNEY DISEASE

We believe that HIV-infected patients with chronic kidney disease should be assessed by using standard clinical tools. The absence of nephrotic-range proteinuria suggests a diagnosis other than HIV-associated nephropathy or glomerulonephritis. The peripheral smear should be examined in patients with acute or chronic renal disease who have thrombocytopenia or hemolysis. A renal biopsy is necessary to diagnose HIV-associated nephropathy. This may be a clinically significant decision for patients in whom highly active retroviral therapy would otherwise be deferred (112) since antiretroviral therapy can improve outcomes, but renal diseases unrelated to HIV infection would not be expected to respond (4, 27, 44, 113). Although this recommendation is not substantiated by evidence from clinical trials, patients with chronic kidney disease associated with HIV infection should be treated with highly active antiretroviral therapy unless it is contraindicated. A good rationale exists for ACE inhibitors for patients who do not have a dramatic response to such therapy, although the effects of such combinations have not been evaluated prospectively. In selected patients whose viral infection is controlled, the addition of glucocorticoids may improve renal function. Further study is necessary to evaluate the results of combinations of antiretroviral therapy, drugs that interrupt the renin–angiotensin axis, and steroids in patients with HIV-associated renal diseases. Renal transplantation is an option for selected patients in controlled trials.

PATHOLOGIC FEATURES OF HIV-ASSOCIATED NEPHROPATHY

Dr. Laura Barisoni (Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, and The Johns Hopkins University, Baltimore, Maryland): The appropriate classification of focal segmental glomerulosclerosis is controversial and evolving. Collapsing glomerulopathy represents a subtype of focal segmental glomerulosclerosis, distinguished by one or more glomeruli manifesting segmental or global collapse and podocyte hypertrophy or hyperplasia (114–117). A common associated feature is severe tubular injury and interstitial inflammatory infiltration out of proportion to the glomerular disease. Collapsing glomerulopathy may be associated with HIV-1 infection, in which case it is termed HIV-associated nephropathy, or it may occur without known viral infection. Although idiopathic collapsing glomerulopathy and HIV-associated nephropathy are similar, HIV-associated nephropathy can be distinguished by the presence of tubular microcysts and glomerular endothelial tubuloreticular inclusions (however, these are not always present). Both forms of collapsing glomerulopathy are believed to share common pathogenic mechanisms related to dysregulation of podocyte phenotype (118, 119).

Like collapsing glomerulopathy, HIV-associated nephropathy is characterized by wrinkling and folding of the glomerular basement membranes (Figure 3, part A). The segmental or global collapse of the glomerular basement membrane is associated with increases in the Bowman
Figure 3. Histopathologic characteristics of HIV-associated nephropathy in humans and transgenic mice.

Human HIV-associated nephropathy: A. A glomerulus shows global collapse of capillary lumina. The glomerular basement membranes are wrinkled and folded, and the urinary space is occupied by proliferating podocytes forming pseudocrescents. Numerous protein reabsorption droplets are present in the podocyte cytoplasm, and this cytoplasm is more abundant than normal (silver staining; original magnification, ×60). B. Tubulointerstitial damage includes interstitial fibrosis with inflammation, tubular atrophy, and microcysts. Eosinophilic casts are present in the dilated tubular lumina (silver staining; original magnification, ×40). C. Ultrastructural analysis shows a collapsed glomerular capillary. Note the wrinkling of the glomerular basement membrane. Podocytes (P) have lost foot processes and primary processes, and their cell body sits directly on the glomerular basement membrane. There is focal detachment of podocytes from the underlying glomerular basement membrane and new matrix deposition (asterisks). (Original magnification, ×8000.) Membrane nephropathy in HIV-1 transgenic mice: D and E. Immunostaining for synaptopodin in wild-type (D) and HIV-1 transgenic mice (E). All the glomeruli are stained for synaptopodin in kidneys from wild type (D). No staining is noted in the kidney of the HIV-1 transgenic mice (E). (Original magnification, ×20.) F and G. Immunostaining for adducin (F) and Na⁺, K⁺-adenosine triphosphatase (G) in HIV-1 transgenic mice: No basolateral staining is noted in this dilated tubule, whereas the nondilated tubules display a delicate basolateral staining (brown). (Original magnification, ×40.)
space. Often this space is partially or globally occupied by large podocytes, with pale cytoplasm containing protein-reabsorption droplets. These cells are arranged in layers around the collapsed areas, forming pseudocrescents. Glomerular damage is associated with tubular atrophy and flattening and regeneration of the tubular epithelium (Figure 3, part B). Interstitial inflammation and fibrosis are generally severe.

In many glomerular diseases, proteinuria is associated with podocyte foot process effacement and reorganization and with condensation of the actin cytoskeleton; the latter manifests as dense intracytoplasmic structures lying adjacent to the glomerular basement membrane. HIV-associated nephropathy podocyte structure is different (Figure 3, part C). Podocytes lose their foot and primary cytoplasmic processes, so the cell body rests directly on the glomerular basement membrane. The actin cytoskeleton is essentially absent. These features resemble those of immature podocytes in the developing glomerulus, supporting the hypothesis that cellular dedifferentiation has occurred. In some cases, podocytes detach and new extracellular matrix deposits fill the resulting space (118).

**Epithelial Cell Phenotype in HIV-Associated Nephropathy**

In all forms of focal glomerulosclerosis and in HIV-associated nephropathy, expression of maturity markers, such as synaptopodin, glomerular epithelial protein 1, podocalyxin, C3b receptor, and common acute lymphoblastic leukemia antigen, is lost in the areas of sclerosis or collapse (Figure 3, parts D and E) (118). In other forms of focal glomerulosclerosis, this phenomenon may result from parietal epithelial cell migration from the Bowman capsule. In HIV-associated nephropathy, this phenomenon may reflect dedifferentiation of podocytes overlying areas of collapse. The loss of actin-based cytoskeleton observed on ultrastructural analysis is reflected by the absence of synaptopodin staining, which also occurs in podocytes overlying noncollapsed glomeruli; this finding suggests that cellular phenotypic alteration precedes glomerular injury. Moreover, podocalyxin, normally expressed in both podocytes and endothelial cells, is lost exclusively in podocytes, suggesting that HIV-associated nephropathy is a selective podocyte disease.

In HIV-associated nephropathy, the podocyte phenotype is not only dedifferentiated but also dysregulated, reflected by loss of expression of Wilm tumor protein 1, a podocyte marker present at all stages of glomerular development (118). In idiopathic collapsing glomerulopathy, dysregulated podocytes may express proteins that are more typically expressed by other cells, such as macrophages, in a process called transdifferentiation (120). Unlike all other diseases characterized by podocyte injury, dysregulated podocytes in patients with HIV-associated nephropathy or idiopathic collapsing glomerulopathy proliferate and also undergo apoptosis (120, 121). The reentry into the cell cycle coincides with the loss of expression of cyclin D1 and cyclin-dependent kinase inhibitors, p27 and p57, together with reexpression of cyclin A and Ki-67 and the de novo expression of p21 (122).

Podocytes have several functions (123). The podocyte slit diaphragm contributes to the glomerular filtration barrier, limiting urinary albumin and large-molecular-weight protein excretion. Podocytes participate in laying down and remodeling the glomerular basement membrane. Podocytes may have structural functions within the glomerulus, maintaining capillary loop structure against both the ballooning force of hydrostatic pressure and the contractile force of mesangial cells. It is not surprising that dedifferentiated podocytes may fail to perform one or more of these functions. Loss of the slit diaphragms (foot process effacement) is associated with proteinuria. The dedifferentiated podocyte may contribute to glomerular collapse by shifting synthesis from collagen IV α3, α4, and α5 chains, typical of the adult glomerular basement membrane, to those typical of its fetal composition (collagen IV α1 and α2 chains), which are present in the glomerular basement membrane in HIV-associated nephropathy. Finally, the pressure of the expanding podocyte cell mass that makes up a pseudocrescent may contribute to capillary loop collapse (Figure 4).

**Epithelial Cells Are a Target of HIV Infection**

The HIV-1 transgenic mouse model of HIV nephropathy, developed at the NIH, directly linked the expression of HIV-1 proteins to altered cellular phenotype (124). HIV-1 transgenic mice develop a renal disease similar to HIV-associated nephropathy, including focal segmental glomerulosclerosis with glomerular collapse, severe tubulointerstitial damage, and tubular microcysts (76). Tubular epithelial cells lose the expression of proteins, such as Na+, K+-adenosine triphosphatase, and adducin (119) (Figure 3,
parts F and G). Two pieces of evidence link HIV gene expression and renal parenchymal changes. In cross-transplant experiments between wild-type and HIV-1 transgenic mice, nephropathy developed only in kidneys transplanted from transgenic into wild-type mice (93). Second, transgene expression was detected in both podocytes and tubular epithelial cells before structural alterations occurred. In renal epithelium, the detection of the transgene is followed by high apoptotic and proliferative indices together with dysregulation of the phenotype, indicating a temporal correlation between HIV-1 expression and nephropathy (121).

HIV-1 gene expression in podocytes and tubular epithelium of multiple nephron segments has been demonstrated in human biopsy specimens (72, 81), suggesting a role of HIV-1 infection in initiating pathogenesis, although the mechanism underlying cellular damage is unknown. To support this hypothesis, recent studies in podocytes derived from HIV-1 transgenic mice indicate a direct effect of HIV-1 gene products on the cell cycle, leading to cellular proliferation (125).

**MECHANISMS OF HIV-ASSOCIATED RENAL INJURY**

Dr. Jeffrey B. Kopp (Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, NIH): The mechanisms by which lentiviruses induce characteristic glomerular and tubular injury are not well understood, but several important clues to pathogenesis have emerged over the past decade.

Opportunistic renal infections might trigger focal segmental glomerulosclerosis. Although it was suggested that *Mycoplasma fermentans* might contribute, few recent data support that hypothesis (126). We showed that the monkey polyomavirus simian virus 40 is recovered more frequently from urinary cells of patients with focal glomerulosclerosis, including idiopathic, collapsing, and HIV-associated variants, compared with patients with other kidney diseases or healthy volunteers (127). These data are insufficient, however, to establish a causal link between simian virus 40 infection and HIV-associated nephropathy.

HIV-1 probably infects lymphocytes and macrophages that enter the kidney, which might release inflammatory lymphokines or cytokines and cause renal injury. Biopsy specimens from patients with HIV-associated nephropathy have a striking increase in renal transforming growth factor-β—producing cells compared with specimens from patients with other forms of focal segmental glomerulosclerosis or other inflammatory glomerular diseases (90, 128). Neither study conclusively identified the cells responsible for producing transforming growth factor-β.

Increasing evidence suggests that HIV-1 may infect renal parenchymal cells, producing cytopathic effects such as proliferation or apoptosis. In vitro experiments demonstrated low-level productive infection of cultured tubular epithelial cells (87, 129). Some investigators have reported infection of cultured mesangial cells (130), while others have not (131). The role of the chemokine receptor GPR1 may be critical (132). In vitro infection of human podocytes, however, has not yet been described. Localization of HIV-1 protein and RNA to renal parenchymal cells has been controversial. Both HIV-1 protein and nucleic acid were found in podocytes and tubular epithelium (44, 133). Recently, Klotman and colleagues (72, 81, 82) developed sensitive in situ hybridization techniques and localized viral RNA and newly retrotranscribed proviral DNA to podocytes and tubular epithelial cells (72, 81). Future work may delineate how HIV-1 infection leads to cellular abnormalities such as proliferation (podocytes) or atrophy and death (tubular epithelial cells).

HIV-1 proteins may directly injure renal parenchymal cells. In humans infected with HIV-1, overt immunodeficiency is not required for development of focal glomerulosclerosis, suggesting that some lentiviral gene product might be responsible for nephropathogenesis. Experiments using HIV-1 transgenic mice show that particular HIV-1 accessory proteins can induce focal segmental glomerulosclerosis and interstitial nephritis (124, 134–136) (Table). These features include focal and segmental collapse and solidification of the glomerular capillary tuft, podocyte hyperplasia (but not glomerular endothelial tubuloreticular inclusions), microcystic tubular dilatation, tubular atrophy, mononuclear interstitial cell infiltration, proteinuria, and progressive renal dysfunction. These transgenic mice do not produce virions (since the *gag* and *pol* genes are lacking from the transgenes), demonstrating that replicating virus is not required for the induction of murine nephropathy. Two lines of evidence suggest that local renal HIV-1 protein production is critical: Transgenic lines that do not express the transgene in the kidney but express it in other tissues do not develop renal disease (124), and nephropa-

### Table. HIV-1 Transgenic Mice with Renal Disease*

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<thead>
<tr>
<th>Study (Reference)</th>
<th>Promoter</th>
<th>HIV-1 Genes</th>
<th>Renal Phenotype</th>
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<tr>
<td>Dickie et al. (124)</td>
<td>Long terminal repeat of HIV-1</td>
<td>env, tat, rev, nef, vif, vpr, vpu</td>
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<td>Hanna et al. (136)</td>
<td>CD4</td>
<td>nef</td>
<td>Interstitial nephritis</td>
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<tr>
<td>Dickie et al. (Unpublished data)</td>
<td>Long terminal repeat of HIV-1</td>
<td>tat, vpr</td>
<td>FSGS</td>
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* Transgenic mice were generated by using the promoter shown (either the long terminal repeat of HIV-1 or the CD4 promoter) and the HIV-1 genes as shown. Mice manifested focal segmental glomerulosclerosis (FSGS) or interstitial nephritis.
Pathogenesis and Treatment of HIV-Associated Renal Diseases

A genetic mutation that contributes to HIV-associated nephropathy might be unique for this syndrome or extend to idiopathic focal segmental glomerulosclerosis or other forms of glomerular injury. While there is no evidence that the first possibility is correct, the relative rarity of HIV-1 infection (<0.2% of the U.S. population is infected) makes it difficult to estimate the risk for HIV-associated nephropathy among different kindreds. However, probands with HIV infection and renal disease have an increased number of first- and second-degree relatives with renal disease (not limited to focal glomerulosclerosis) compared with ethnically matched patients with HIV-1 infection without kidney disease (62). These data tend to support the second or third possibility outlined. At present, it seems that HIV-associated nephropathy probably has both genetic and environmental components.

We have initiated ongoing studies comparing genetic polymorphisms among African Americans with HIV-associated nephropathy, idiopathic focal segmental glomerulosclerosis, and HIV-1 infection for at least 8 years but without renal disease (a hypernormal control group, in that these individuals have been challenged with a virus known to induce focal glomerulosclerosis but have not developed this syndrome), African-American blood donors, and European-American patients with idiopathic focal segmental glomerulosclerosis and blood donors. We have performed genotyping in these individuals for polymorphisms in various candidate genes, including those for chemokine receptors, chemokines, and members of the renin–angiotensin–transforming growth factor-β system. To date, preliminary studies demonstrate that the only gene that differs between African-American patients with HIV-associated nephropathy and African-American controls is the gene encoding ACE (138). Patients homozygous for an Alu insertion in intron 16 of ACE are at an increased risk for focal segmental glomerulosclerosis; this is true for both African Americans with HIV-associated focal segmental glomerulosclerosis and those with idiopathic focal segmental glomerulosclerosis. In European Americans, the ACE polymorphism was not significantly associated with focal segmental glomerulosclerosis.

Angiotensin-converting enzyme polymorphisms have been associated with the incidence or rate of progression of various glomerular diseases, including diabetes (139), IgA nephropathy (140), and idiopathic focal segmental glomerulosclerosis (141, 142) in Asian patients, but all these studies suggest that patients homozygous for the intron 16 deletion allele are more susceptible. Of interest, these studies have included few African Americans. Unlike other populations, in African Americans, there is no correlation between intron 16 polymorphism and serum ACE level (143). We interpret these data to suggest that, in African Americans, the intron 16 polymorphism is in linkage disequilibrium with one or more mutations that contribute to focal segmental glomerulosclerosis risk.

Host Genetic Variation and the Development of HIV-Associated Nephropathy

People of African descent with HIV-1 infection are at a markedly increased risk for focal segmental glomerulosclerosis, with an at least 18-fold increased risk compared with people of European descent (137). Since a similar predilection is seen in the United States, Europe, and South America, cultural factors seem an unlikely explanation. Instead, one or more host genetic loci probably contribute to risk, with particular risk alleles more common in populations of African descent. Theoretically, these alleles might contribute to HIV-1 entry into renal parenchymal cells, potentiate toxicity of viral accessory proteins in renal cells, or heighten a fibrotic response to viral-initiated renal injury.

A provisional summary of these data suggests that the viral regulatory or accessory proteins Tat plus viral protein R (Vpr), or Vpr acting alone, may induce focal glomerulosclerosis, and Nef (negative factor for viral replication) may contribute to interstitial nephritis. These viral proteins have complex effects on host cell function. Dissecting the mechanisms of renal injury induced by these proteins is an area for future research. Tat is a transactivating protein that increases viral RNA production. Vpr has many effects on host cells, including G2 cell cycle arrest, regulation of apoptosis, and cytokine production, and acts as a transcriptional coactivator or corepressor, depending on the genetic context. Nef downregulates CD4 expression. In summary, in mice, particular viral regulatory or accessory proteins induce many characteristic functional and histologic changes of HIV-associated nephropathy.

Viral genetic variation might contribute to the epidemiology of HIV-associated nephropathy, explaining why only some patients develop renal disease. Partly because of the relatively high error rate of HIV-1 reverse transcriptase, the HIV-1 genome is highly plastic and many viral quasi-species exist. The env (envelope) gene encodes the transmembrane glycoprotein (gp) 41 and the associated gp120. gp120 first binds CD4, inducing a conformational change in gp120 that facilitates its binding to one of several coreceptor molecules, which function as chemokine receptors in the host. CD4 independent cell infection has also been described. The receptors responsible for viral entry into renal parenchymal cells have not been well characterized. CD4 has not been convincingly demonstrated on any renal parenchymal cell in vivo, although RNA has been reported in cultured tubular epithelial cells. Mesangial cell infection may be dependent on GPR1 (132). Particular viral variants may have mutations in gp120 that facilitate entry into renal cells or have mutations in regulatory or accessory proteins, such as Vpr or Nef, with particular toxicity for renal cells, but few data address this issue.
CONCLUSIONS

Much has been learned about the pathogenesis and treatment of HIV-associated renal diseases because of the development of animal models and the molecular evaluation of clinical samples. Although the pathogenesis of HIV-associated nephropathy is clearly linked to the viral illness, over the next decade we must determine how infection results in the development of disease. HIV peptides rather than infection may be more important in nephropathogenesis. We must determine why some patients are susceptible to disease development and others are not. Genetic factors, the host response, and effects of HIV peptides on podocytes, on renal cellular apoptosis, and on the ability to present antigen may be critical to pathogenesis. Although highly active antiretroviral therapy will play an important role in preventing and treating HIV-associated nephropathy, well-designed and controlled clinical trials are necessary to determine the roles of therapy with glucocorticoids and ACE inhibitors. Knowledge about the treatment of HIV-infected patients with renal transplantation and proper treatment of other HIV-associated renal diseases is rudimentary.

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References


Focal segmental glomerulosclerosis in primates infected with a simian immunodeficiency virus.  
Ross MJ, Klotman PE.  


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