Human immunodeficiency virus-associated glomerulosclerosis

The epidemic of human immunodeficiency virus (HIV) infection and the clinical picture of acquired immunodeficiency syndrome (AIDS) have revealed characteristic involvements of most organs and organ systems, including the kidneys. Abnormalities in fluid, electrolyte, and acid-base metabolism in patients infected with HIV-1 have been recognized and are the subjects of recent reviews [1, 2]. However, most attention has focused on a distinct pattern of structural renal disease that has come to be termed HIV-associated nephropathy (HIVAN). This article will summarize the features of this entity, emphasizing those aspects most relevant to the practicing clinician.

Structural renal disease in patients infected with HIV

Although some early descriptions of renal involvement in patients with AIDS documented a variety of parenchymal lesions mostly involving glomeruli and characterized clinically by proteinuria, these publications did not suggest a specific pattern of involvement [3, 4]. However, in 1984 two separate reports drew attention to patients in New York and Miami with proteinuria and evidence of focal and segmental glomerulosclerosis (FSGS) on renal biopsy [5, 6]; in addition, the report from Miami found a large number of patients in whom mesangial prominence was the primary histologic abnormality [6]. The authors from Downstate Medical Center in New York went to some length to distinguish HIV-associated FSGS from that arising as a result of intravenous heroin use, so-called heroin nephropathy, since many of their AIDS patients were intravenous drug users [5]. They pointed out that progressive loss of renal function occurred at a much more rapid pace in patients with HIVAN than in those with heroin nephropathy despite the similarity in renal histologic lesions. However, the report from Miami did not find a high incidence of rapidly advancing renal failure, perhaps because their population included a large number of patients whose main histological abnormality was mesangial expansion rather than FSGS [6, 7].

These two centers updated their experience in 1987. At Downstate Medical Center, 10% of AIDS patients had rapidly advancing renal failure; on renal biopsy, most had FSGS [8]. As a group these patients did very poorly; of those enrolled in dialysis therapy, only a small number left the hospital. The Miami group drew attention to the propensity for HIVAN to affect certain groups of AIDS patients [9], as will be discussed. As this clinical experience mounted, the following picture of the components of HIVAN began to emerge. Patients with HIVAN have proteinuria, usually in the nephrotic range, and sometimes massive in magnitude. This is accompanied by renal insufficiency, which often rapidly progresses to end-stage renal disease (ESRD), within three to six months, requiring treatment by means of dialysis. Other clinical features observed frequently, but by no means universally, include the presence of kidneys which are normal to increased in size when examined by diagnostic ultrasound despite being highly echogenic [10], the frequent absence of peripheral edema expected from the nephrotic proteinuria [11, 12], and the infrequency of hypertension accompanying the renal failure [13]. The increased kidney size and echogenicity are thought to relate to some of the pathologic features of this entity (see below). The explanation for the absence of edema in some patients despite high-grade proteinuria is not known; although it has been suggested that it may reflect the wasted, catabolic, and possibly volume-depleted state of many of these patients [11, 12], other wasted conditions such as kwashiorkor are accompanied by edema. The unusually low incidence of hypertension in this group of patients despite advanced renal insufficiency was documented by Bourgeoisie and colleagues [13]. Of 100 patients with HIVAN seen at their institutions, diastolic blood pressure exceeded 100 mm Hg in only 15, which easily responded once these patients underwent treatment with dialysis. Although the diagnosis of HIVAN is usually made in patients with already identified AIDS-defining diagnoses, cases have been observed in asymptomatic HIV-infected patients, in whom the renal biopsy was felt to be sufficiently characteristic to lead to HIV testing of the patients [13–15].

Epidemiology of HIVAN

As this clinical picture of HIVAN developed, the identification of certain associated risk factors soon became apparent. Patients from Downstate Medical Center in Brooklyn with HIVAN shared three features in large measure: they were African-American, male, and most were intravenous heroin users [5, 8]. Thus, black race, male gender and injection drug use as a mode of HIV transmission were thought to be major risk factors for the development of HIVAN. This was supported by experience in Miami, where patients with HIVAN were 50% of injection drug users (most of whom were black males) and much less commonly male homosexuals [9]. A high incidence of HIVAN was also observed in another center in New York [11], and a composite review of published experience as of 1990 identified 27% of patients with HIVAN to have intravenous drug use as a risk factor [16].

Because of the seeming association of HIVAN with injection drug use, we queried whether HIVAN was indeed a specific entity or merely reflected the occurrence of heroin-associated nephropathy in African-American injection drug users who coincidentally were infected with HIV. The experience at San Francisco General Hospital indicated that HIV-infected patients had a variety of clinical and histologic abnormalities of the kidneys, although those progressing to ESRD were likely to be of black race and to have injection drug use as a risk factor for HIV transmission; only some of these could have had HIVAN [17]. As discussed below,
HIVAN and heroin-associated nephropathy share certain histologic features, and the latter is also a disease of black males [18]. Thus, some question was raised regarding the nature of clinical renal disease in patients infected with HIV-1. This early experience from San Francisco General Hospital did not support the existence of a specific HIV-related renal syndrome [17].

Subsequent clinical observations appear to have resolved this conflict. Overall, well less than half of reported cases of HIVAN have had injection drug use as a risk factor for HIV transmission [16, 19]. Moreover, it has also occurred in Haitians, where HIV infection occurs through heterosexual transmission, and in children of HIV-infected mothers, where vertical transmission accounts for HIV infection [9, 20]. However, the great majority of reported cases have been of sub-Saharan African origin or descent [16, 19, 21]. Thus, the mode of HIV transmission does not appear to be a major risk factor for the development of HIVAN, while black race has become evident as an important component of this entity. More recent experience from San Francisco General Hospital is consistent with this [22]. We have observed an increased rate of referral of HIV-infected patients with structural renal disease to our Division, many of whom had HIVAN on clinical grounds although not undergoing renal biopsy. These patients have been African-American, and this increase is related to an increasing incidence of African-Americans with AIDS both in the City of San Francisco and receiving treatment at San Francisco General Hospital [22].

The reasons why black race may confer particular susceptibility to HIVAN are not known. It may reflect a more general susceptibility of African-Americans to all forms of kidney disease, the basis for which is not currently understood [23, 24]. African-Americans are also disproportionately victimized by AIDS [25], although the high prevalence of HIVAN in African-Americans compared to whites suggests that a specific interaction of HIV and black race must be responsible. African-Americans exhibit a different humoral response to HIV-1 p24 antigen than whites [26], and could have other differences in the response to HIV-1 infection that relates to the development of HIVAN. This interaction could have a true genetic basis or could relate to a variety of socioeconomic and cultural factors such as access to health care, diet, and toxin exposure. The role of gender in risk for HIVAN is more difficult to assess. Although most reported cases have been in males, so have most reported cases of HIV infection. Further study will be necessary to determine if male gender is a separate risk factor for the development of HIVAN.

Pathology of HIVAN

The histological picture of HIVAN is characteristic [14, 15, 26–29]. The primary lesion is that of focal sclerosis of glomerular tufts, with early involvement reflected by segmental distribution of the sclerosis and later by global sclerosis. Glomerular capillary walls are collapsed and retracted, leading to occlusion of lumens in the areas involved in the sclerotic process. Cellular proliferation in glomeruli does not occur, but swelling of visceral epithelial cells is common (Fig. 1). Mesangial expansion is seen in less advanced cases and may be a forerunner of the sclerotic process, although it may represent a separate clinical entity. A marked degree of interstitial fibrosis occurs, felt in most cases to be out of proportion in severity to the degree of glomerular involvement. This is accompanied by patchy foci of mononuclear cell infiltrates. Cystic tubular degeneration is widespread, with dilated tubular lumens filled with proteinaceous eosinophilic material. A variable degree of tubule cell necrosis has also been observed. Immunofluorescent examination of renal tissue has shown deposition of immunoglobulins, chiefly IgM, and complement components primarily in the areas of glomerular sclerosis with lesser staining in the mesangium. The casts in tubular lumens contain immunoglobulins, complement, light chains, albumin, and fibrin, but not Tamm-Horsfall protein, although this protein is found in hyaline casts in adjacent, undilated tubules [14]. Electron microscopic changes confirm the glomerular sclerotic process and show widespread effacement of foot processes of the visceral epithelial cells. Characteristic tubuloreticular inclusions have been observed with high frequency in glomerular and peritubular capillary endothelial cells and invading leukocytes in the interstitium, and are regarded
Fig. 2. High-powered transmission electron micrograph showing tubuloreticular structures in perinuclear cisterns in a glomerular endothelial cell of a patient with HIVAN. ×14,000. From [28] with permission of the authors.

As an important pathologic feature of HIVAN, within the cells, these inclusions have been identified in smooth and rough endoplasmic reticulum and in cisternae of the Golgi apparatus (Fig. 2). Since these tubuloreticular inclusions are thought to reflect a cellular response to viral infection [30], they have contributed to speculation about the pathogenesis of HIVAN (see below). Glomerular electron dense deposits have also been seen with some regularity. These are thought to represent immune complex formation or deposition; since FSGS is ordinarily not regarded as an immune complex mediated glomerulonephritis, their occurrence may reflect another process(es). Attention has been drawn to the occurrence of intranuclear bodies [27, 28]; however, their significance has not been established.

As commented above, this pathologic picture has been viewed as sufficiently characteristic as to warrant description as “a unique combined glomerular, tubular, and interstitial lesion” [14] which on occasion has led to the recognition of HIV-1 infection after the fact [14, 15]. None of these pathologic features is seen only in HIVAN; many are also observed in heroin-associated nephropathy, including interstitial fibrosis and tubuloreticular inclusions [31, 32], and there are many causes of FSGS [33]. Nevertheless, the constellation of these histologic and ultrastructural changes warrants characterization as a distinct pathological entity [12, 34]. The higher frequency and severity of these changes of HIVAN, coupled with the occurrence of this entity in patients with HIV-1 infection who have no history of injection drug use (vertical transmission from mother to child, heterosexually transmitted infection, infection from transfusion of contaminated blood products), argue that the lesion is specifically related to HIV-1 and not to some aspect of injection drug use. The clinical course of the two entities also differs in some respects: more rapid progression to ESRD, relative lack of hypertension, and preservation of normal to enlarged kidney size are characteristic of HIVAN [8, 12, 13], whereas heroin-associated nephropathy progresses more slowly, is accompanied regularly by hypertension, and leads to small, shrunken kidneys [4, 8, 35].

Although the clinical and histologic features of HIVAN may permit its distinction from heroin-associated nephropathy, its specificity and uniqueness for HIV-1 infection have been challenged. In a retrospective autopsy review of children dying with immunodeficiency disorders (7 AIDS, 13 with severe combined immunodeficiency, 6 with other forms of immunodeficiency), Foster and colleagues observed some of the renal changes of HIVAN, including FSGS, tubular ectasia and dilatation, and tubular epithelial cell injury, in patients without HIV-1 infection [36]. They suggested that the renal pathologic changes may reflect the consequence of infection with some other virus(es). Although provocative, this study suffers from its retrospective nature and the lack of electron microscopic examination of kidney tissue. Recent attention has also been drawn to a severe collapsing form of FSGS, resembling HIVAN in most respects, in a group of adult patients without HIV infection or known HIV risk factors [37]. Thirteen of 16 were African-American, most had nephrotic proteinuria, and half progressed to ESRD or death within five months. This picture resembles closely the picture of HIVAN except that the patients gave no evidence of HIV infection. Renal tissue also failed to reveal endothelial tubuloreticular structures on electron microscopic examination [37]. This study underscores the relationship between black race and severe FSGS, but also calls into question the specificity of the lesion of HIVAN.
The occurrence of other forms of glomerular pathology, coupled with the presence of glomerular electron-dense deposits in kidneys of patients with HIV-1 infection, has led to the hypothesis that HIV-infected patients may be at risk for immune complex glomerulonephritis distinct from the FSGS of HIVAN. Particular attention has been drawn to the occurrence of IgA nephropathy, although nephritis associated with IgG deposition also occurs [38–42]. Interestingly, many of these patients have also had tubuloreticular inclusions detected on electron microscopy of renal biopsy specimens [38–40]. The immune complexes present in the circulation and renal tissue in these cases have involved HIV-1 antigens. The clinical presentation of these cases has differed somewhat from cases of HIVAN in that the severity of the proteinuria is variable and the clinical course more benign (Table 1) [39, 40]. The occurrence of membranous nephropathy secondary to chronic hepatitis B virus infection in the setting of HIV infection has also been noted [43], as has the development of a nephrotic syndrome due to secondary syphilis [44]. Other glomerular lesions reported in AIDS patients include minimal change nephropathy, membranoproliferative glomerulonephritis, and a lupus-like diffuse proliferative glomerulonephritis [12, 17, 41]. The relationship of these lesions to the HIV-1 (or other) infection is not established.

The major clinical features of HIVAN, mesangial hyperplasia, and immune complex glomerulonephritis are distinguished in Table 1. The predilection for white race, more moderate proteinuria, presence of hematuria, and slow clinical progression differentiate IgA nephropathy from HIVAN [45], but the few cases of IgG immune complex disease do not permit ready generalization. Relative to HIV-related FSGS and mesangial hyperplasia, the immune complex glomerulonephritides are uncommon. Nochy and associates observed a marked degree of interstitial fibrosis and scarring in some of their patients with immune complex disease [41], a finding also observed by Kimmel et al [40], and indicating a mixed picture of immune complex disease with elements of HIVAN.

**Pathogenesis of HIVAN**

Although the mechanisms leading to renal disease in patients infected with HIV-1 have not been fully elucidated, considerable progress in this area has occurred in the past few years as a result of studies in animal and cell culture models and clinical studies in patients. It is appealing to speculate that human renal cells can become infected with HIV-1. The initial report of Cohen et al demonstrated viral genome and p24 protein in glomerular and tubular epithelial cells of human renal biopsy specimens using *in situ* hybridization and immunocytochemistry [46]. The failure of another study to demonstrate viral antigens in kidney tissue of patients with HIVAN is probably explained by a low viral burden in their patients and the relative insensitivity of these methods [47], since polymerase chain amplification has shown viral genome to be present in kidneys of patients with HIVAN [48]. Mice transgenic for a noninfective HIV-1 construct develop a renal syndrome that closely resembles HIVAN in humans: they manifest proteinuria and nephrotic syndrome as well as rapidly advancing renal failure. The kidneys show FSGS, microcystic tubular dilatation, and interstitial fibrosis as well as the accumulation of laminin, type IV collagen and heparan sulfate proteoglycan, all components of the extracellular matrix [49]. When probed with a cDNA designed to hybridize with all proviral mRNA's, viral genes were found to be expressed in the kidneys of these transgenic mice [49]. Thus, renal infection with this HIV-1 construct, and expression of its genes, led to the development of a renal lesion that bears a striking similarity to the clinical picture of HIVAN, making it attractive to speculate that HIVAN itself results from direct infection of renal cells by HIV-1.

The situation is probably not that simple. Kimmel and associates used polymerase chain amplification of microdissected tissue to show that glomeruli, tubules, and infiltrating inflammatory cells from HIV-1-infected patients nearly uniformly contained viral genome, and this was true whether or not the patients had clinical evidence of renal disease or histologic evidence of FSGS [48]. These authors consequently suggested that the development of HIVAN required a “triggering mechanism” in addition to viral infection of renal tissue. The nature of such a triggering mechanism is not known. To the extent that the transgenic mouse model reflects human HIVAN, it must also be present in the mice, and could conceivably be related simply to dose of virus or numbers of infiltrating inflammatory cells. Alternatively, it could reflect a difference between latent viral infection and the actual expression of viral peptides. It could also have a connection to genetic background in view of the high proportion of black patients with HIVAN, as discussed above. It is also far from established that productive infection with HIV-1 occurs in renal tissue or is related to the development of renal disease. The observation just cited by Kimmel and colleagues of viral genome in kidney tissue of AIDS patients without any evidence of nephropathy [48] raises the possibility that this material could be an “innocent bystander” with no causal relationship to the development of tissue damage. *In vitro* studies are equivocal. Green, Resnick and Bourgoignie
provided evidence that glomerular mesangial and endothelial cells, but not epithelial cells, in culture could be infected with HIV-1 [50]. Of note, Cohen and Nast showed viral genome to be present in epithelial but not mesangial cells of human renal biopsies of patients with HIVAN using in situ hybridization [14]. However, Alpers, McClure and Bursten were unable to demonstrate infection of human mesangial cells in culture by several strains of HIV-1 and HIV-2, although they did not use coculture techniques that might have allowed detection of low level infection [51]. These investigators also found no evidence of CD4 expression, the putative portal of entry of HIV into the cell, in their mesangial cell cultures [51]. An alternative possibility is that HIV-infected macrophages take up residence in the kidney to initiate a sequence of events leading to HIVAN [48, 52]. It is also possible that elevated levels of cytokines, known to occur with HIV-1 infection, may reach the kidneys via the circulation to cause organ damage, although this mechanism by itself does not appear adequate to account for the occurrence of HIVAN in certain specific risk groups.

The mechanisms by which HIV-1 infection leads to renal disease are not established but this topic has been the subject of a recent editorial review in this journal [53]. An attractive hypothesis is that HIV-1 infection of renal cells results in increased synthesis of transforming growth factor-β (TGF-β). This cytokine has been associated with fibrotic disease in other organs, and is linked to glomerulosclerosis in numerous models of experimental renal disease [54]. It possesses the remarkable property of stimulating its own synthesis, and has profound effects on the extracellular matrix: it induces the synthesis of numerous matrix proteins, it down-regulates the synthesis of proteases acting on matrix proteins, and it stimulates the expression of integrins, important in matrix formation, on the cell surface [55]. These properties make it appealing to suggest that HIVAN results from unchecked synthesis of TGF-β following renal infection with HIV-1 which then leads to fibrotic renal disease characterized by FSGS and interstitial scarring and fibrosis. In support of this, preliminary reports have indicated that TGF-β is significantly increased in tubules of the transgenic mouse model [56], and in glomeruli and the tubulointerstitium in kidney biopsies from patients with HIVAN compared to disease controls or normal kidneys [57, 58]. A recent study has also shown that incubation with TGF-β of human mesangial cells transfected with the HIV-1 long terminal repeat (LTR) leads to increased expression of viral genes [59]. The LTR contains regulatory sequences that stimulate viral transcription [53]. Thus, one may speculate that renal infection with HIV-1 initiates accelerated production of TGF-β and possibly other cytokines [60]. TGF-β, in addition to a positive feedback on its own synthesis, also stimulates viral replication. A vicious cycle is established whereby viral infection is rapidly increased within the kidney and extracellular matrix formation is driven by ever higher levels of TGF-β. Such a scheme could account for the widespread glomerular and interstitial sclerosis seen in kidneys of patients with HIVAN as well as the rapidly advancing renal failure which occurs as a result of it. TGF-β also causes hypertrophy of cultured rat mesangial cells [61], perhaps offering an experimental analog for the mesangial prominence seen in some patients with HIVAN [8, 9, 13]. Further investigation should establish whether this hypothesis has merit. It is unlikely, however, that a TGF-β-mediated mechanism accounts for HIV-associated mesangial hyperplasia, since this lesion runs a more benign course [45] and is not associated with widespread glomerular and interstitial fibrosis. It is also possible that HIV may reach the kidney through invasion of CD4-positive lymphocytes/macrophages to initiate the renal lesion [12, 52]. In addition, elevated levels of circulating TGF-β have been observed in patients infected with HIV-1 [62, 63], and could play a role in the pathogenesis of the renal abnormalities of HIVAN. Consistent with this, sera from HIV-1-infected patients, and supernatants from cultures of infected macrophages, stimulated mesangial cell proliferation and matrix production [64]. TGF-β would be a candidate mediator of these effects. These relationships are schematized in Figure 3.

Other disease mechanisms may also exist to account for impaired renal function in HIVAN. Langs and associates felt that renal functional deterioration was more severe than expected from examination of renal biopsy material in a group of patients with HIVAN [29]. They consequently speculated that hemodynamic changes could be contributing to the reduced GFR in their patients. If so, this would at least offer the hope that some intervention might correct the hemodynamic abnormality and lead to an improvement in renal function. However, that has not been the experience to date (see below). Patients infected with HIV-1 who have immune complex glomerulonephritis may also develop advanced renal insufficiency [40, 41]. Renal biopsies in these patients show components of HIVAN as well as immune complex deposition [40, 41], and the renal insufficiency cannot clearly be attributed to one or the other process. Mechanisms by which immune complexes affect the kidney have been recently reviewed [65]. One report has linked renal infection with a rare mycoplasma organism (Mycoplasma fermentans incognitus) to HIVAN [66], although further work will be necessary to establish the connection between this opportunistic infection and the development of the renal abnormalities of HIVAN. Finally, the possibility exists that other viruses may infect patients with HIVAN and be related to the development of the renal disease. HIV-1-infected patients have a high incidence of hepatitis virus infection, and injection drug users are more likely to be infected with human T-cell lymphotropic virus types I and II [67, 68]. However, with the exception of the recognized link between hepatitis virus infection and glomerular disease [69–71], the relationship between infection and renal disease, particularly FSGS, has not been established.

**Treatment and role of renal biopsy**

At the present time, no therapeutic intervention has been shown to have any benefit in arresting the progression of HIVAN. In part this is due to the (usually) rapid progression to end-stage renal disease (ESRD) limiting the time available for treatment regimens, and in part it relates to the reluctance of most clinicians to expose already immune-compromised HIV-1 infected patients to therapeutic programs involving further immunosuppression for other than short periods of time. Some evidence indicates a benefit of long-term (several months) treatment with glucocorticoids in the management of idiopathic FSGS [72, 73], and a recent report indicates that HIVAN may also respond to corticosteroid treatment with an improvement in renal function and reduction in proteinuria [74]. The steroid treatment was related to the development of an opportunistic infection in one patient, but was well tolerated in the others. Although the follow-up period was short, and the number of patients small, this report opens up the
possibility that some patients with HIVAN may benefit from steroid therapy with an acceptably small risk of exacerbating their underlying immune compromise. Further trials are warranted to evaluate this treatment, and the NIH is developing a prospective trial of prednisone in patients with HIVAN. More general measures also raise major treatment dilemmas. The possible value of a protein-restricted diet in arresting the progressive renal failure, although controversial [75, 76], poses serious problems for the AIDS patient, in whom nutritional wasting is common and an important goal of therapy is maximum nutritional support. Recently, it has been suggested that treatment with zidovudine ameliorates progressive HIVAN for a period of time [77–79]. This has been based for the most part on anecdotal case reports in individual patients and on a retrospective review. A preliminary report of a larger series of patients from Downstate Medical Center showed a better outcome in zidovudine-treated patients compared to historical controls [80]. However, not all patients in the treated group had evidence of HIVAN whereas all of the historical controls were taken from an ESRD population, so this study cannot answer the question of efficacy of this agent in patients with HIVAN. If HIVAN does indeed result from renal infection with HIV-1 as suggested above, then a benefit of zidovudine, at least initially, might be expected much as this agent has benefit in the generalized manifestations of HIV-1 infection.

The absence of proven effective therapy for HIVAN opens the question of the value of renal biopsy in such cases. While the decision regarding renal biopsy is always an individual one, several general issues bear on the decision. First, a variety of glomerular abnormalities in addition to FSGS have been observed in HIV-1-infected patients, as summarized earlier, so the possibility that one of these other lesions could account for the renal presentation must be entertained. A few cases of minimal change nephropathy
and other steroid-responsive lesions have been observed [12, 81, 82], at least one of which responded to short-term steroid therapy without evident exacerbation of the underlying HIV-1 infection after 16 months of follow-up [82]. In addition, steroid therapy may prove to have a role in HIV-associated FSGS, as discussed earlier [74]. Thus, renal biopsy helps to identify such patients, in whom a treatment option exists. Second, a renal presentation of HIVAN may be the initial clue to HIV-1 infection; in such patients, renal biopsy may well be the stimulus leading to testing for HIV-1 infection. Third, asymptomatic patients with HIV-1 infection and proteinuric renal disease may benefit from the prognostic value of the definitive renal diagnosis based on renal biopsy. Fourth, patients with AIDS are also at risk for the development of acute renal failure [8, 12, 13, 17, 83]; although usually readily distinguishable on clinical grounds, renal biopsy may occasionally play a role in this setting. Finally, the patient’s own wishes regarding his or her desire to know the exact pathological diagnosis will also figure importantly in the decision to carry out a renal biopsy.

Because of the uniformly poor outcome of HIVAN to date, it is desirable to identify other lesions which may follow a somewhat better course. As discussed earlier, features favoring HIVAN include typical ultrasonographic features of the kidneys, nephrotic-range proteinuria, a bland urinary sediment, and the absence of serologic markers of renal disease, while stable renal function with nephrotic or low-grade proteinuria, kidneys of normal echogenicity on ultrasound examination, hypertension, a nephritic urinary sediment, and hypocomplementemia, a positive antinuclear antibody test, or other serologic abnormality, may all suggest the presence of a renal disease other than HIVAN (Table 1). Patients certainly exist who do not fall into one or the other of these categories, and biopsy may be the only means to identify the precise nature of the renal lesion. Renal biopsy is consequently of value in approaching patients with renal involvement in the setting of HIV-1 infection [42].

Experience has shown that patients with HIV-1 infection who develop acute renal failure have a high likelihood of recovery and should therefore be supported with hemodialysis if needed until renal function is restored [8, 12, 13, 35, 84].

**HIV and ESRD**

Given the rapid and unrelenting loss of renal function in HIVAN, and absence of any clearly effective treatment, most patients will progress to end stage and require dialysis treatment. This has been an area of some controversy, for several reasons. There has been a real question whether dialysis is an effective treatment option in this setting. The initial reports indicated a very poor outcome in patients with overt AIDS and HIVAN treated by means of hemodialysis [8, 85], with few patients with opportunistic infections surviving on dialysis more than six months. The possibility exists that opportunistic infections may actually progress more rapidly in hemodialyzed patients [12, 13, 86]. Although this initial dismal outcome may have improved somewhat with recent advances in overall care of the AIDS patient, most nephrologists have come to expect only limited benefits with outpatient hemodialysis of patients with AIDS and opportunistic infections. This bleak outlook has stimulated discussion about whether hemodialysis should even be offered to such patients [84, 86, 87]. Again, although no mandate exists, arguments favor offering support with hemodialysis for those informed patients with advanced AIDS who request it [84, 86, 87].

The situation is much better in less advanced stages of HIV-1 infection. Patients with asymptomatic infection or AIDS-related complex (ARC) do not deteriorate rapidly when placed on hemodialysis: in the series by Ortiz and associates [85], 28 patients with asymptomatic HIV-1 infection entered the hemodialysis program. Of these, 7 died of non-HIV-related causes, and 7 others progressed to ARC or AIDS after 276 ± 81 days of dialysis. The remaining 14 remained asymptomatic and alive on hemodialysis 488 ± 75 days after commencing dialysis treatment. Thus, less severe stages of HIV-1 infection carry a better prognosis on hemodialysis.

Recent studies paint a similar picture for treatment with peritoneal dialysis of ESRD in HIV-infected patients. Survival is shorter in infected patients than noninfected patients treated with this modality, and outcome is related to the stage of the HIV infection [88, 89]. Infected patients had a higher rate of peritonitis than noninfected controls in one series [89] but not others [88, 90]. Theoretical arguments have been advanced for advantages of peritoneal dialysis over center-based hemodialysis [91]. These include the possibility that the former may cause less impairment of immune defense, and less stimulation of HIV-1-infected T-cells, provide enhanced nutritional support through glucose absorption from the dialysate, and result in higher hematocrits, enabling increased use of marrow-suppressing antiretroviral agents such as zidovudine. To these theoretical advantages are added the more generally accepted ones of reduced blood exposure and transmission of infection. Drawbacks of peritoneal dialysis in AIDS patients include the loss of albumin with each exchange, the possibility of more frequent peritonitis, and a high rate of technique failure [89, 90]. Technique failure usually results from progression of AIDS-related illnesses to the point where self-care is no longer feasible. Serum albumin was a marker for morbidity complications in a general group of CAPD patients [92], and a low serum albumin also correlated with shortened survival in another group of HIV-infected patients with ESRD treated with either peritoneal dialysis or hemodialysis [90].

Renal transplantation in HIV-1-infected patients with ESRD is also a complex area. Experience is not large and is mostly retrospective and anecdotal. It now appears clear that HIV-1 can be transmitted by an infected organ [12], so that patients with high risk behavior for HIV-1 infection are generally excluded as organ donors [93]. Whether infection with HIV-1 should exclude a patient from being considered as a transplant recipient has not been established. Although case reports document the rapid evolution of AIDS and early death in some recipients, attributed to the immunosuppressive regimens employed to combat transplant rejection, there are other examples where infected patients have tolerated immunosuppression for long periods of time [93]. It is the position of a National Kidney Foundation-National Institutes of Health task force that asymptomatic HIV-1 infection should not deny consideration for transplantation and that transplantation continue to be a treatment option for ESRD in such patients until such time as it has been clearly established to be contraindicated [94].

A number of other issues pertain to the management of the ESRD patient with HIV-1 infection that are beyond the scope of this Perspective. They include the risk of transmission of the virus...
in the dialysis setting, the techniques of infection control in the dialysis unit, the question of testing of dialysis patients for HIV-1 infection, and dosing adjustments for AIDS-related medications in the ESRD patient. The interested reader is referred to the several excellent articles and reviews dealing with these topics [84, 86, 90, 94–96].

Summary

The constellation of nephrotic proteinuria, FSGS, and rapid loss of renal function in a patient infected with HIV-1 has been sufficiently widespread and well documented to justify identification as a specific renal syndrome, HIV-associated nephropathy. The position paper of the National Kidney Foundation-National Institutes of Health task force estimated in 1990 that 10,000 to 15,000 persons will develop renal disease in association with AIDS [94]. Management of these patients is complex, and many will reach ESRD and require dialysis treatment, posing additional care problems. Greater understanding of the pathogenesis of the renal disease should lead to treatments which will forestall the reach ESRD and require dialysis treatment, posing additional costs.

15,000 persons will develop renal disease in association with AIDS [95]. The position paper of the National Kidney Foundation-National Institutes of Health task force estimated in 1990 that 10,000 to 15,000 persons will develop renal disease in association with AIDS [94]. Management of these patients is complex, and many will reach ESRD and require dialysis treatment, posing additional care problems. Greater understanding of the pathogenesis of the renal disease should lead to treatments which will forestall the reach ESRD and require dialysis treatment, posing additional costs.

References

34. Bourgoignie JJ, Menees R, Parvo V: The nephropathy related


84. RAO TKS: Maintenance dialysis in patients with human immunodeficiency virus infection. Semin Dial 1:203–208, 1988