HIV Infection and The Kidney

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Since the advent of the AIDS pandemic in the late 1970s and early 1980s, over 1 million AIDS cases have been reported to the World Health Organization (1). Accounting for underdiagnosis and inadequate reporting, an estimated 18.5 million adults and 1.5 million children worldwide have become infected with the human immunodeficiency virus (HIV). The incidence of new HIV infection in underdeveloped countries of sub-Saharan Africa and South and Southeast Asia continues to grow at an alarming rate (1). In 1995 alone, there were an estimated 2.5 million new cases of HIV infection in Southeastern Asia and almost 2 million new cases in sub-Saharan Africa (2). In industrialized countries, the number of deaths from AIDS over the last year has roughly equaled the number of new HIV infections. Through the middle of 1994, there have been over 240,000 deaths from AIDS in the United States, with over 40,000 new cases reported annually. Some cities such as New York have reported many thousands of AIDS cases, and up to 500,000 persons in the New York metropolitan area have been reported to be infected with the virus. Many studies have found populations of intravenous drug abusers (IVDA) to have a 60 to 85% carriage rate for HIV.

At the inception of the HIV pandemic in the early 1980s, it appeared that the kidney might be spared from major complications of the disease. However, in 1984, reports of renal involvement in AIDS patients first appeared. An early report documented the spectrum of renal involvement in HIV-infected patients (3). In a histopathologic study of a small group of AIDS patients with proteinuria or renal insufficiency, a variety of renal lesions was found, including acute tubular necrosis, focal interstitial nephritis, nephrocalcinosis, renal cell carcinoma, cryptococcal abscess, and a variety of glomerular lesions (3). A subsequent autopsy study from the Columbia Presbyterian Medical Center in New York confirmed the heterogeneous nature of the histopathologic lesions seen in AIDS patients (4). This population of 26 men and four women, with a mixed racial background and a mean age of 39 yr, included patients with diverse risk factors for AIDS, including homosexuality, intravenous drug abuse, and a history of blood transfusions. These patients had multiple opportunistic infections and AIDS-related neoplasms typical of this patient population. Of the 30 consecutive AIDS patients coming to autopsy, 16 had evidence of acute tubular necrosis, 13 had no evidence of renal histopathologic findings, and only one had the classic glomerular lesion of HIV-associated nephropathy. In 1984, the same year that featured the initial descriptions of renal disease occurring in AIDS patients, a detailed account of a distinctive pattern of sclerosing glomerulopathy was first reported in AIDS patients in New York City from King’s County Medical Center/Downstate in Brooklyn (5). This report, which consisted largely of black drug abusers and which emanated from the same institution and the same group of investigators that first clearly documented the occurrence of heroin nephropathy 10 yr earlier, was initially met with considerable skepticism in geographic locales where the HIV-infected population consisted predominantly of white homosexuals (6). Although there was concern that this entity merely represented the older heroin nephropathy now seen in HIV-infected IVDA, this initial report, and others, subsequently confirmed the unique clinical features and histopathologic manifestations of HIV-associated nephropathy (7-23). Subsequent studies documented the frequent occurrence and significance of acute renal failure in the HIV-infected population (7,24,25). The development of ESRD in significant numbers of HIV-infected patients who may require dialytic support or the potential for transplantation has thrust a number of ethical and therapeutic challenges on the renal community. More recently, studies describing the potential mechanism(s) of HIV-related renal disease and the use of newer therapeutic agents to treat HIV-associated nephropathy have given new hope for prolonged survival in this population (26).

Acute Renal Failure

The course of acute renal failure in patients with AIDS has been described by a number of investigators (7,14,17,24,25, 27). Rao et al. described the course of 23 such patients and Valeri and Neusy reviewed 88 episodes of acute renal failure in almost 450 AIDS patients in New York City (7,24). Acute renal failure in both series was most often the result of acute tubular necrosis, and the most common precipitating factors in both studies included medications (pentamidine, aminoglycosides, trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory drugs) and dehydration superimposed on sepsis, hypotension, and respiratory failure. Other series have also noted similar predisposing etiologies (8,18,27). In the study by Rao et al., all six patients with mild renal failure regained renal function. Of those 17 patients with severe renal failure (serum creatinine concentration >6 mg/dL), eight of the 11 who did not undergo dialysis died in renal failure, whereas five of the remaining six who were dialyzed regained renal function (7).
Some of these patients survived for up to 24 months after recovery of renal function. Other early series also noted a high incidence of acute renal failure in AIDS patients, either documented clinically or by the autopsy findings of acute tubular necrosis (4,11). In these early series, episodes of acute renal failure were usually preterminal events. Valeri and Neusy performed a retrospective chart review of 449 patients with AIDS who were admitted to Bellevue Hospital in New York over a 3-yr period (24). Almost 20% (88 patients) developed an acute deterioration of renal function as defined by a rise in serum creatinine concentration to >6 mg/dL, volume depletion accounted for one third of cases and baseline renal insufficiency was common (12 of 21 cases). Over one half of these patients died during the course of that hospital admission, with the highest mortality rate among those developing sepsis or shock. In the survivors, recovery of renal function was virtually complete, except when nephrotoxic antimicrobials were the cause of the renal failure. Recently Rao and Friedman compared the course of 146 HIV-infected patients with severe acute renal failure (including 132 with overt AIDS and 14 with asymptomatic HIV seropositivity) to a group of 306 contemporaneous non-HIV-infected subjects with severe acute renal failure (25). Sepsis was directly or indirectly responsible for 75% of the cases of acute renal failure in the HIV-infected group, but only 39% in the control population. In contrast, urinary obstruction was a cause of acute renal failure in 17% of the control subjects, but in none of the HIV-infected population. The HIV-infected patients were younger (91% less than 50 yr of age versus 33% in the control group) and in worse medical condition, often limiting intensive dialysis intervention (36% agonal and not dialyzed versus 18% in the control group). The mortality rate, even in the dialyzed AIDS patients, was similar to that of the older population without AIDS who developed acute renal failure (60% versus 56%). These data indicate that acute renal failure secondary to acute tubular necrosis is a frequent occurrence in HIV-infected patients and is usually related to nephrotoxins, sepsis, hypotension, and dehydration. Although it is potentially reversible with dialytic support, acute renal failure nonetheless carries a high mortality.

HIV-Associated Nephropathy

Epidemiology

Most studies of HIV-associated nephropathy originated from large urban East Coast centers, including New York (3,4,7–10) and Miami (11–14), with reports of smaller numbers of patients from other U.S. cities (15–22). Whereas the prevalence of HIV-associated nephropathy is over 90% among HIV-positive nephrotic patients in these East Coast centers, it is only 2% in San Francisco, where most seropositive patients are white homosexuals (21,22).

A review of over 200 patients with HIV-associated nephropathy found that 90% were black, 70% male, and 50% IVDA (23). This predominance among blacks is all the more striking if one considers that in the United States, HIV infection is three times more common among whites than blacks (23). To address the issue of whether this was related to the larger representation of heroin abusers among black HIV-infected patients, Bourgoignie et al. computed the racial incidence of HIV-associated nephropathy among non-IVDA worldwide (28). Among 88 non-IVDA with HIV-associated nephropathy, the black:white ratio was roughly 12 to 1, slightly more than the ratio of 5 to 1 noted among IVDA. These data indicate a striking racial predominance of blacks in HIV-associated nephropathy independent of intravenous drug abuse. There is a similar strong racial predominance among black children with perinatal HIV infection, in whom IV drug abuse is obviously never a risk factor (13,17).

HIV-associated nephropathy is also more severe in the black population. In a Miami-based population of non-IV-drug abusing, HIV-infected adults with glomerular disease, 17% of Caucasians studied had an extremely mild form of focal glomerulosclerosis, 75% had diffuse mesangial hyperplasia (DMH), and none had severe focal segmental glomerulosclerosis (FSGS) (28). This contrasted with Caribbean and American blacks, in whom 55% had severe focal sclerosis, 9% had mild focal sclerosis, and only 27% had diffuse mesangial hyperplasia. A similar distribution toward more severe glomerular lesions was also noted among American blacks in Los Angeles (29). These morphologic differences were reflected in clinical presentations, with blacks more likely to manifest nephrotic-range proteinuria (>3.5 g/24 h) and renal insufficiency (serum creatinine concentration >3 mg/dL), whereas whites often had subnephrotic proteinuria and serum creatinine values under 2 mg/dL (28). The cause of this strong racial predilection among blacks is unknown. A similar tendency toward glomerulosclerosis has been reported in blacks with hypertension, diabetes, heroin nephropathy, and rapidly progressive “collapsing” forms of idiopathic focal segmental glomerulosclerosis (30,31). Although HLA predominance has been identified in certain populations with idiopathic FSGS and heroin nephropathy (32,33), HLA risk factors have not yet been identified in HIV-associated nephropathy. The larger glomerular volume in blacks (versus whites) has been proposed as a factor predisposing to glomerulosclerosis (34,35). Our understanding of the causes of this racial predominance of HIV-associated nephropathy among blacks is clearly inadequate and may provide an ideal population in which to study potential genetic risk factors for glomerulosclerosis.

Although IV drug abuse constitutes the HIV risk factor in 50% of these patients with HIV-associated nephropathy, the disease has been described in virtually all HIV-risk groups or situations, including homosexuals, perinatally acquired HIV infection, heterosexual transmission, exposure to contaminated blood products, and Haitians. The low incidence of HIV-associated nephropathy in Europe presumably reflects the region’s small black population (36–38). In the largest European study (from Paris), among 60 HIV-infected patients (29 black, 31 white), 84% of renal biopsies in blacks disclosed FSGS, compared with only 11% in whites (39–40). Among the white patients in this study, 71% were homosexual and 26% IVDA, compared with 12% and 17%, respectively, in the black group. Heterosexual exposure was presumably the most common risk factor in this black population, which consisted primarily of immigrants from Central Africa and the Caribbean.
findings indicate that the differences in prevalence of HIV-associated nephropathy between Europe and the United States are likely the results in large part of racial factors.

HIV-associated nephropathy may occur at any stage of HIV infection. In one New York–based study, onset of nephropathy was most common in otherwise asymptomatic HIV-infected patients (8). Thus, the term HIV-associated nephropathy is preferred to that of AIDS nephropathy. Among 26 HIV-infected patients with biopsy-proven FSGS, 12 were asymptomatic carriers, eight had AIDS-related complex (ARC) and only six had clinical AIDS (7). The greater incidence of nephropathy early in the course of HIV infection has also been noted by others (23). Because these patients lack systemic manifestations, the role of renal biopsy in the diagnosis of HIV infection assumes particular importance in this group.

The incidence of HIV-associated nephropathy in autopsy- and biopsy-based studies varies according to the geographic location, biopsy indications, and pathologic criteria for diagnosis. In a New York AIDS autopsy study, histologically confirmed HIV-associated nephropathy was present in one of 30 patients (3.3%) (4). In Miami, FSGS was present in 24 of 240 autopsies of HIV patients (10%) (41). Others have reported incidences at autopsy of 1 in 50, 1 in 91, 7 in 77, and 3 in 210 (18,22,37,42). Valeri and Neusy estimated a 7.6% prevalence of nephropathy among 449 hospitalized AIDS patients at Bellevue Hospital in New York City (24). There has been no relationship between the development of nephropathy and patient age, duration of HIV infection, or types of opportunistic infections (23).

**Clinical Features and Clinical Course**

Several studies have described the clinical features of patients with classic HIV-associated nephropathy (5,7,8,14,20,23,24). Presenting features typically include proteinuria, usually in the nephrotic range, and renal insufficiency. In a study from Columbia-Presbyterian Medical Center in New York, 26 patients with HIV-associated nephropathy at presentation had a mean urinary protein excretion rate of 6.6 g per day and mean serum creatinine concentration of 5.4 mg/dL (range, 1.1 to 17.4 mg/dL) (7). In this series, most patients had the full nephrotic syndrome, with edema (in 62%), a low serum albumin level (mean, 2.2 g/dL), and an elevated serum cholesterol level (mean, 246 mg/dL). In some series, despite the high frequency of nephrotic-range proteinuria and hypoalbuminemia, only a small percentage of patients had hypercholesterolemia (24), and edema has been uncommon (14). These features may reflect disease leading to reduced hepatic synthesis of lipoprotein precursors. At presentation, subnephrotic proteinuria has been noted in some patients, as have microscopic hematuria and sterile pyuria as well (8,24). Hypertension (defined as diastolic pressure ≥100 mm Hg) was present in almost 40% of patients in one series, but has been far less prevalent in several other published reports (7,20,24). Indeed, in one series of 100 nephrology consultations in HIV-infected patients with clinical renal disease, 87% of the patients were either normotensive or hypotensive (14). This was true despite the presence of severe renal insufficiency in some patients, and the nephrotic syndrome and renal insufficiency in others. By ultrasonography, the kidneys of patients with HIV-associated nephropathy have typically been enlarged and highly echogenic (8,14). In one study, despite the fact that most patients had already reached end-stage renal failure, the mean size of each kidney was 12.3 cm by ultrasound (8). In some instances, echogenicity has correlated with the development of microcystic tubular dilation, rather than particular glomerular changes or severity of proteinuria (14).

The course of HIV nephropathy is usually a rapid progression to renal failure. In an early study, Rao et al. found the mean time from diagnosis to uremia was 3 to 4 months for HIV-nephropathy patients with a creatinine clearance rate at diagnosis of over 60 mL/min, versus 43.7 months for heroin-nephropathy patients with a similar clearance rate (5). Even in heroin nephropathy, patients with a creatinine clearance rate of less than 20 mL/min at diagnosis, the time to the onset of uremia was as long as 7 months. In a second study, Rao et al. followed-up 55 AIDS patients with HIV nephropathy; ten were lost to follow, two died without uremia, and 43 progressed to uremia (7). Of these 43, the 12 who were not dialyzed all died; 31 were given dialytic support and 26 of these patients died within 3 months of initiating dialysis. These poor outcomes in the dialyzed population contributed to the initial skepticism regarding the value of dialysis support in the population with HIV nephropathy and overt AIDS in the pre-antiviral therapy era (vide infra).

In a study from our unit at Columbia-Presbyterian Medical Center in the pre-AZT (zidovudine) era, the course to renal failure was extremely rapid and patient survival varied according to the stage of HIV infection (8). Median time to dialysis was only 10.9 wk, with a minority of patients displaying a much slower course to renal failure of up to 78 wk. Median survival from diagnosis of renal disease to death was 4.5 months (range, 3 wk to 3 yr). Asymptomatic carriers had the longest survival (median, 9.7 months) compared with 3.6 months for patients with ARC and 1.9 months for patients with clinical AIDS at the time of onset of nephropathy. Death resulted from inanition and infectious or neurologic complications of AIDS; the presence of nephropathy per se did not negatively influence patient survival when compared with that of a group of AIDS patients with comparable systemic manifestations but without nephropathy. Clearly the status of the patients’ HIV infection, rather than the presence of renal disease per se, had the greatest impact on survival. This study suggested that patients with asymptomatic or early HIV infection and HIV-associated nephropathy could have prolonged survival. Subsequent studies have indicated an even greater prolonged renal survival relative to earlier reports. These findings suggest that better supportive care and perhaps reduction of viral burden by antiretroviral drugs may exert a beneficial effect on the course of nephropathy (vide infra).

**Nephropathy in HIV-Infected Children**

Whereas FSGS is the predominant lesion described in 83% of adult HIV-infected patients undergoing renal biopsy, this is not the case in children (23). Overall, FSGS accounts for only 50% (31 of 62) of glomerular disease among HIV-infected children, and the course to renal failure tends to be more
protracted than that in adults (44). Of 28 children with perinatal AIDS reported from Miami, eight (29%) had renal involvement, including four with FSGS and the nephrotic syndrome and four with diffuse mesangial hypercellularity and mild proteinuria (12). All eight were black or black/hispanic. In a subsequent study of 155 children with AIDS, Strauss et al. reported 12 (7.7%) with nephrotic range proteinuria, of whom five had FSGS, five mesangial hyperplasia, one segmental necrotizing glomerulonephritis suggestive of lupus nephritis, and one with minimal change disease (13). The mean age at diagnosis of focal sclerosis was 27 months, and 38 months in the five patients with diffuse mesangial hyperplasia. The average time to severe renal failure was 9 months (range, 1 to 22 months) and the mean time from onset of nephropathy to death was 15 months (range, 2 to 29 months). No patient died as a result of renal causes. In a follow-up study, 556 HIV-positive pediatric patients presenting between 1981 and 1993 were evaluated (45). Using a permissive definition of nephropathy as persistent abnormal proteinuria (albustix ≥ 1+ in ≥ two urine specimens ≥2 wk apart in the absence of fever or positive blood cultures), 72 (12.9%) fulfilled criteria for HIV-associated nephropathy. Of these 72 patients, 19% developed renal insufficiency. Of 37 renal biopsies performed, only 14 showed focal sclerosis, 13 diffuse mesangial hypercellularity, five minimal change lesion, two focal and segmental necrotizing glomerulonephritis, two hemolytic uremic syndrome, and one acute tubular necrosis (46). These findings reinforce the earlier observations that focal sclerosis is less common in pediatric HIV-infected patients than in adults. Children with the focal sclerosis form of HIV nephropathy also appear to have frequent electron-dense deposits by electron microscopy (47,48). Of five pediatric patients with glomerular disease reported from New Jersey, two had FSGS, one DMH, and two proliferative glomerulonephritis with mesangial immune deposits (49). In a study from New York City of 66 children with perinatal HIV-infection, 38 developed renal disease but only one was nephrotic. Proliferative glomerulonephritis was present in 14 of 16 patients on renal histologic examination, and FSGS as the sole lesion was present in only one biopsy specimen (48). Abundant mesangial immune deposits were present in seven cases (48). These data from diverse geographic regions of the United States suggest that lesions other than focal segmental sclerosis, such as mild mesangial proliferative forms of glomerulopathy and immune-mediated glomerulonephritis, are more frequent in pediatric than adult patients with HIV infection.

Pathology of HIV-Associated Nephropathy

The term HIV-associated nephropathy should be reserved for the typical histopathologic form of FSGS and potentially related mesangiotrophies (such as DMH and minimal change disease). It should not be applied indiscriminately to the diverse immune deposit glomerular diseases and non-immune deposit glomerular diseases that have been reported in this population.

Although some centers have reported a high incidence of glomerulonephritis with immune deposits in HIV-infected patients, a review of 112 renal biopsies obtained from HIV-infected patients accessioned by the Columbia University nephropathology laboratory disclosed 104 of 112 (94%) with glomerular disease, from whom 73 (65%) biopsies revealed FSGS and six (5%) minimal change disease (Table 1) (39,50). A pattern of DMH as described by the Miami group has not been observed with any frequency in our New York population, among whom focal segmental sclerosis remains the most prevalent glomerular lesion.

Characteristic histologic features of HIV-associated nephropathy include a collapsing form of FSGS (4,9) (Figure 1). The term "collapse" refers to an implosive retraction of the glomerular basement membrane with resulting occlusion of glomerular capillary lumina, either segmental or more commonly global in distribution (Figure 2). The involved segments show virtually no increase in mesangial or intracapillary matrix, and hyalinosis is usually absent. An important component of this lesion is striking hypertrophy and hyperplasia of the overlying visceral epithelial cells, which form a cellular corona over the collapsed lobules. The visceral cells may display enlarged vesicular nuclei, mitotic figures and numerous intracytoplasmic protein resorption droplets (Figure 3). Studies using antibody to PCNA (proliferation cell nuclear antigen) have revealed a high proliferative rate for podocytes, which may even display mitotic figures (51) (Figure 4). Other glomeruli may show more classic lesions of FSGS, with increased matrix, discrete segmental scars, hyalinosis, and capsular adhesions. When renal biopsies of HIV-associated nephropathy are compared with biopsies of heroin nephropathy and idiopathic FSGS and matched for serum creatinine and level of proteinuria, a larger percentage of collapsed glomeruli, less glomerular hyalinosis, and greater visceral cell swelling and droplet formation are present in HIV-associated nephropathy (4).

An important component of HIV-associated nephropathy, which often appears out of proportion to the degree of glomerular disease, is a collapsing fibrillary lozenge that is often associated with focal sclerosis. A high proliferative rate for podocytes is also a characteristic of HIV-associated nephropathy, and these cells may even display mitotic figures. These features, along with abundant mesangial immune deposits, may resemble those of idiopathic FSGS. However, HIV-associated nephropathy is not characterized by the presence of immunoglobulin A deposits and mesangial immune deposits, as seen in some cases of idiopathic FSGS. Furthermore, patients with HIV-associated nephropathy typically have higher serum creatinine levels and are more likely to develop end-stage renal failure than those with idiopathic FSGS. The presence of these findings in the biopsy specimen suggests a diagnosis of HIV-associated nephropathy.

Table 1. Renal biopsies in HIV-positive patients at Columbia-Presbyterian Medical Center (N = 112)*

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<tr>
<th>Glomerular Disease (93%) (N = 104)</th>
<th>Tubulointerstitial Disease (7%) (N = 8)</th>
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<tr>
<td>Focal Segmental Sclerosis, 73</td>
<td>Interstitial Nephritis, 5</td>
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<tr>
<td>Membranoproliferative GN, 10</td>
<td>Drug-Induced Disease, 2</td>
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<tr>
<td>Minimal Change Disease, 6</td>
<td>Idiopathic, 3</td>
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<td>Amyloidosis, 3</td>
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<td>End-Stage Kidney Disease, 1</td>
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*GN, glomerulonephritis; IgA, immunoglobulin A.
Figure 1. Low-power view of HIV-associated nephropathy showing two glomeruli with global tuft collapse and one obsolescent glomerulus. There is prominent tubulointerstitial disease, including interstitial edema, fibrosis, and inflammation. (Jones Methenamine Silver; original magnification, ×125).

Figure 2. Collapsed glomeruli have predominantly global wrinkling and retraction of the glomerular basement membranes with marked podocyte hypertrophy and hyperplasia. (Jones Methenamine Silver, original magnification, ×500).

Figure 3. Visceral epithelial cells are markedly hyperplastic forming a pseudocrescent that fills the urinary space. The visceral cells contain large numbers of intracytoplasmic protein resorption droplets. (Periodic acid-Schiff, original magnification, ×500).

Figure 4. A mitotic figure (arrow) is seen within a visceral epithelial cell. (Periodic acid-Schiff, ×800).

ulerosclerosis, is severe tubulointerstitial disease including prominent tubular degenerative and regenerative features, interstitial edema, fibrosis, and inflammation with frequent but variable tubular atrophy. When compared with biopsies of patients with heroin nephropathy and idiopathic FSGS, there is more prevalent and severe tubular degenerative and regenerative changes (4). The interstitial infiltrate consists largely of lymphocytes, with a predominance of CD8+ T cells, and fewer plasma cells, monocytes, and B cells. Another common finding is microcystic dilation of tubules, containing loose proteinaceous casts consisting of albumin and immunoglobulins, but not Tamm-Horsfall protein, suggesting the presence of an ultrafiltrate of plasma occurring in a setting of nonselective proteinuria (19) (Figure 5). Similar dilations can be seen involving Bowman’s capsule.

Recently, a distinctive form of acute interstitial nephritis known as DILS (diffuse infiltrative lymphocytosis syndrome) has been described in HIV-infected patients. This is a systemic illness affecting a minority of HIV-infected patients that is characterized by interstitial infiltration of salivary glands, lung, gastrointestinal tract, and kidney by an inflammatory infiltrate rich in CD8 T cells (102,103). Renal manifestations are often accompanied by Type IV renal tubular acidosis. A genetic predisposition to the syndrome has been provided by the finding of HLA DR5 allele DRB1*1102 or the HLA DR6 allele DRB1*1301 in 67% of 38 individuals, compared with 29% of control subjects (odds ratio = 8.2) (104).

By fluorescence microscopy, there is frequent staining for IgM, C3 and, less commonly, C1 in areas of glomerulosclerosis as well as in the mesangium of nonsclerotic glomeruli.
Visceral cell protein resorption droplets frequently positive with antisera to IgG, IgA, and albumin, and should not be misinterpreted as glomerular immune deposits.

Electron microscopy shows that the areas of glomerular collapse consist of wrinkled and retracted segments of glomerular basement membrane (Figure 6). Visceral cell hypertrophy, microvillus transformation, and extensive foot process effacement are observed over both sclerotic and nonsclerotic segments. In a minority of cases, glomeruli may contain sparse small electron-dense deposits in the mesangium or along the peripheral glomerular capillary wall in subendothelial or epimembranous locations (Figure 7). Some biopsies with collapsing sclerosis by light microscopy are found by immunofluorescence and electron microscopy to contain more substantial mesangial or peripheral capillary wall immune deposits that are positive for IgG or IgA or both. These likely represent superimposition of an immune complex–mediated glomerulonephritis on preexisting FSGS. It is our own impression that these cases with overlapping features have a natural history similar to HIV-associated nephropathies that have no immune deposits. Over 90% of biopsies of HIV-associated nephropathy demonstrate numerous tubuloreticular inclusions (TRI) within glomerular and other vascular endothelium (4) (Figure 8). Similar inclusions may also be present in the cytoplasm of infiltrating lymphocytes and rarely in visceral epithelial cells. These inclusions often referred to as “interferon footprints,” can be induced in vitro in normal lymphocytes by exposure to alpha-interferon. They consist of 24-nm interanastamosing tubular structures located within dilated cisternae of endoplasmic reticulum. Their number often exceeds one per glomerular capillary and they are sometimes multiple in a single cell, as observed frequently in patients with systemic lupus erythematosus. Other ultrastructural features of HIV-associated nephropathy include granular degeneration of the nuclear
chromatin of interstitial and tubular cells (Figure 9), cytomembranous inclusions, cylindrical confronting cisternae, and increased numbers of nuclear bodies (Figure 10) (4,9).

The relationship of diffuse mesangial hypercellularity to FSGS within the spectrum of HIV-associated nephropathy is controversial. Some reports have stressed the presence of mesangial hyperplasia (12), whereas mesangial alterations are absent in others (4). Moreover, many cases of DMH and minimal change disease in the setting of HIV infection have associated interstitial inflammation, a feature not observed in the idiopathic forms. We have seen an example of HIV-associated diffuse mesangial hypercellularity evolve into FSGS on repeat biopsy (4). The milder mesangial lesion is more common in children and whites and is usually accompanied by less severe proteinuria. It is likely that the entities of HIV-related DMH and focal segmental sclerosis form a histopathologic continuum similar to that proposed for idiopathic nephrotic syndrome resulting from minimal change disease and focal segmental sclerosis.

**Pathogenesis**

Because HIV-associated nephropathy commonly occurs before opportunistic infections are manifest, infections per se do not appear to play a role in the development of nephropathy. Glomerular immune deposits are generally absent in HIV-associated nephropathy, making it unlikely that antibody-mediated injury constitutes the primary pathogenetic event. Moreover, because only a minority of HIV-infected patients develop nephropathy, a particular subset appears to be at risk. These observations suggest unique viral-host interactions, which depend both on stimulating features of the virus and the individual nature of the host response. Proposed mechanisms of HIV nephropathy could follow any of several schema (Figure 11): (1) direct injury to renal epithelial (visceral and tubular cells) by cytopathic effects of viral infection of renal parenchymal cells; (2) indirect injury to the kidney by renal cellular uptake of circulating virally encoded molecules; or (3) indirect injury to the kidney through release of cytokines by infected lymphocytes or monocytes in the circulation or infiltrating the kidney.

The final common pathway in the development of HIV-associated nephropathy is likely to involve alterations in the patterns of gene expression of renal parenchymal cells by cytokines and growth factors, leading to interstitial fibrosis and enhanced glomerular matrix synthesis. It is likely that the nature of the host response to viral infection is critical to the development of nephropathy. HLA-linked responses particular to a subset of blacks may explain some of the epidemiologic features of HIV-associated nephropathy. For example, considerable genetic heterogeneity has been described among blacks in North America and the Caribbean and may be traced to different geographic origins in Africa. There may also be biological heterogeneity in the strains of HIV-1 that could account for a particular renotropic or "nephritogenic" strain.
For example, isolates of HIV-1 may vary in their tropism, replication rates, and syncytium-producing capacity (52–54). Strains isolated from asymptomatic individuals are more often monocyte-tropic and slowly replicating, whereas isolates from patients with fully developed AIDS are more often T-tropic or monocyte/T-tropic and generally replicate rapidly (55–57). It may be that monocyte-tropic strains characteristic of early disease states have greater capacity to produce nephropathy. It is also possible that genetic differences in HIV strains may be critical. HIV strains from different parts of the world may vary by as much as 15% at the level of nucleotide sequence (55). The B clade, for example, is predominant in North America, whereas the G and H clades are prevalent only in Europe. Differences in the genetic sequence of HIV-1 could account for the existence of strains with greater renal tropism. There is also evidence that HIV infection does not progress uniformly in different organs within an infected individual. For example, studies of env sequence have revealed 5 to 10% sequence variability between viruses infecting pulmonary macrophages and peripheral blood monocytes (58). These studies suggest an anatomic compartmentalization of viral evolution that may explain susceptibility to nephropathy in only a subset of patients.

It has been proposed that HIV may directly infect renal parenchymal cells, although data are conflicting (59–63). A proposed target for direct infection is the glomerular mesangial cell, which shares many features with monocytes and has been shown to bear possible HIV membrane receptors, the CD4 antigen and FcR (64). In rodents, monocytes may comprise up to 3% of the normal mesangial cell population (65). Thus, HIV-infected hematopoietic cells residing within the glomerulus might provide a local reservoir for HIV. Investigations into the infectivity of human glomerular cells in vitro have yielded conflicting results (61,62). HIV has been shown to infect and replicate in glomerular endothelial cells and, to a lesser degree, in mesangial cells, but not in visceral epithelial cells (61). A clinical monocyte-tropic strain, but not a high-passage laboratory T-tropic strain was capable of infecting mesangial cells, whereas both strains were equally infective to glomerular endothelial cells. Because the experimental protocol utilized DEAE-dextran, which is capable of disrupting cellular membranes, it may have bypassed the physiologic route of receptor-mediated infection, and thus may not be directly relevant to the in vivo situation (26). On the other hand, Alpers et al. were unable to demonstrate productive infection of human mesangial cells by either T-tropic or monocyte-tropic strains of HIV-1 or HIV-2 (62). Although one study demonstrated viral genome in tubular and visceral epithelial cells of renal biopsies of HIV-associated nephropathy by in situ hybridization using a c-DNA probe, and immunostains for p24 antigen, these data have not been confirmed by others (60,66). Moreover, immunohistochemical stains for viral proteins p24, p17, gp41, and gp120 are extremely unreliable in formalin-fixed, paraffin-embedded tissue (60). Recently, by use of microdissection techniques on renal biopsies, the HIV genome has been identified by polymerase chain reaction in glomerular cells, tubular cells, and infiltrating leukocytes in 22 of 28 HIV-infected patients with nephrotic syndrome, whether as a result of focal segmental sclerosis, immune complex-mediated glomerulonephritis, or other diverse conditions (63). These results, if accurate, suggest that direct viral infection of the kidney is common but not sufficient to cause nephropathy, and other cofactors may be necessary.

Our understanding of the pathogenesis of HIV-associated nephropathy has been aided by the development of a transgenic model that lacks a 3.1-kilobase fragment of the HIV genome, overlapping gag that encodes for the structural (nucleocapsid-core) proteins, and pol, which encodes for the enzymes (reverse transcriptase, integrase, and ribonuclease), but preserves the genomic structure of the HIV envelope and regulatory genes (67–69). Heterozygous transgenic mice from three of eight founders developed a form of nephropathy characterized by focal segmental sclerosis, with mesangial hypercellularity, visceral cell hypertrophy, interstitial inflammatory infiltrates, and tubular microcysts. Proteinuria, first detectable at 24 days of age, progresses to nephrotic syndrome and ESRD. Modest expression of viral RNA was demonstrated in renal tissue at early stages before the onset of nephropathy, and became almost undetectable at 60 days. Rev protein was the only virally encoded protein that could be identified in glomeruli, although it is not certain whether this resulted from endogenous synthesis or trapping in the course of glomerular filtration. These findings suggest that productive virus in the kidney may not be necessary to produce nephropathy. Rather, renal uptake of viral gene products may induce nephropathy through transactivation of host genes, either through direct effects of viral gene products on target cells or indirectly through the release of cytokines. Subsequent work implicates upregulation of basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-β) in this model (70). Interestingly, transgenic renal tubular epithelial cells grown in vitro manifest features of transformed cells, with greatly enhanced proliferative capacity that could mediate tubular microcyst formation (70). The viral gene products that are operative in this model have not yet been identified. Candidate viral proteins include
Viral Infection of:

- Kidney Parenchymal Cells
- Intrarenal Lymphs/Monos
- Circulating Lymphs/Monos

- Cytopathic Effects
- Elaboration Viral Gene Products
- Induction Host Cytokines

Glomerulosclerosis

Figure 11. Hypothetical pathogenesis of HIV-associated nephropathy.

tat, which can be released by virally infected cells and endocytosed by various cell types (71). Tat induces bone marrow macrophages to upregulate production of TGF-β (72) and glial cells to increase synthesis of collagen and fibronectin in vitro (73). In other systems, HIV infection can dysregulate a variety of host cytokines, including IL-1, IL-6, tumor necrosis factor alpha and granulocyte macrophage-colony stimulating factor, any of which could be important in the development of nephropathy (74). The curious fact that only three of eight founder transgenic lines developed nephropathy emphasizes that expression of viral gene products \textit{per se} is not sufficient to produce nephropathy, and susceptibility to nephropathy may depend on individual host responses.

\textbf{Treatment}

The optimal treatment of HIV-associated nephropathy remains unknown. There have been no randomized controlled trials to define the benefits of any form of therapy. Uncontrolled studies have reported benefits of treatment in terms of reduction of proteinuria, improved renal survival, or both with a variety of medications. In general, these therapies have included one of three major forms of treatment: antiviral therapy, immunosuppressive medications, and nonspecific methods to reduce proteinuria.

Several case reports and nonrandomized trials report potential benefit from antiviral therapy in HIV-associated nephropathy (75,76,77). There is one report of a remission of the nephrotic syndrome in a patient with biopsy-documented HIV nephropathy treated with AZT (78). A second report describes remission of the nephrotic syndrome in an AIDS patient and presumed HIV nephropathy (no biopsy) treated with AZT and acyclovir (79). There are also cases in which AZT was said to have improved the GFR of HIV-nephropathy patients (80). A retrospective analysis of 54 HIV-infected patients, largely IVDA with clinical proteinuria, of whom 43 received AZT, suggested a delay in the progression to ESRD with treatment (76). Fourteen percent of AZT-treated patients and a similar percent of nontreated “control” HIV patients were azotemic at presentation. In the AZT-treated group at 2 yr follow-up, nonazotemic patients had an excellent prognosis, with only 14% developing mild azotemia and 32% remaining nonazotemic. Of the initial group of azotemic patients receiving AZT, however, four progressed to ESRD in a few months and two others had a marked increase in azotemia (76). Of the 11 HIV patients not treated with AZT, five progressed to ESRD. These data suggest that use of AZT might be beneficial if given early in the course of HIV nephropathy. Likewise, a prospective study of 15 patients with HIV-associated nephropathy treated with AZT and compared with historical control subjects suggested a benefit from therapy (75). Others have also reported a beneficial effect with reduction in the incidence of nephrotic syndrome or slowing of the rate of decline in renal function or both with AZT and an acceleration in the rate of progression to renal failure once the AZT was discontinued (77,81). It is likely that the response to antiviral therapy depends upon the stage of the nephropathy or the status of the HIV infection. Vigorous therapy in patients with early histologic lesions and milder degrees of proteinuria and renal dysfunction at the initiation of therapy may be more efficacious. Likewise, current guidelines for the treatment of HIV infection recommend measurement of the viral load and use of two or more antiviral agents rather than treatment with AZT alone (82). It is unknown whether newer antiviral therapy or combination therapy, especially if used early in the course of the disease, may ameliorate or even reverse the course of HIV-associated nephropathy. A recent study to evaluate the benefits of ACE inhibition in HIV-associated nephropathy documented the independent benefits of antiviral therapy in preventing the progression to renal failure (83). Three of the treated patients received recently released antiretroviral drugs.

Immunosuppressive therapy, including both corticosteroids and cyclosporine, has been used to treat HIV-associated nephropathy (47,84,85). An isolated report describes a remission of the nephrotic syndrome in an HIV-seropositive white man
who had a renal biopsy showing diffuse mesangial hypercellularity, but not the classic clinical picture or biopsy pattern of HIV nephropathy (84). Prednisone treatment has been tried in at least two series of children with HIV-associated renal lesions and the nephrotic syndrome, without a favorable response (44,47). Although we have seen complete remission of proteinuria in HIV-infected children with the minimal change pattern on biopsy, we have not had any patient with the sclerosing HIV-associated nephropathy respond fully to corticosteroid treatment (unpublished observations). However, a recent study documented the course of HIV nephropathy in 12 HIV-infected children with the minimal change pattern (44,47). Although we have seen complete remission of proteinuria in at least two series of children with HIV-associated renal lesions (85,86). Eleven had plasma creatinine levels, >2.5 mg/dL and nine had over 2 g of protein daily. The mean serum creatinine concentration decreased from 9.2 to 5.4 mg/dL, and proteinuria was reduced in six patients from an average of 7.8 to 3.7 g daily. Interestingly, two patients who had been on dialysis at the beginning of the study were able to discontinue dialysis after steroid therapy. Nevertheless, after 10 months of follow-up, two patients had died and four others reached ESRD, whereas some patients suffered serious infections, including cytomegalovirus retinitis and Mycoplasma avium intracellular. Although there are few reports of repeat renal biopsies in steroid-treated patients, improvement in renal function appears to correlate best with reduced interstitial inflammation and tubular damage (87). An isolated report recently noted that cyclosporine therapy led to the complete remission of the nephrotic syndrome in three pediatric HIV-nephropathy patients with classic lesions of HIV-associated nephropathy (47). These children remained in remission as long as cyclosporine was continued.

Recently, angiotensin-converting enzyme (ACE) inhibitor therapy has been used in small numbers of nephrotic HIV-infected patients, resulting in a reduction in proteinuria (83,88–90). Serum ACE levels have been found to be elevated in HIV patients, and it has been suggested that this enzyme may play a pathogenetic role in the development of glomerulosclerosis through modulation of mesangial cell growth and matrix synthesis (91). A patient with biopsy-proven HIV-associated nephropathy and the nephrotic syndrome treated with the ACE inhibitor fosinopril experienced a reduction in proteinuria without deterioration of renal function (88). After discontinuation of the drug, proteinuria returned to pretherapy levels. Other trials utilizing various ACE inhibitors in small numbers of HIV-infected patients with and without nephropathy, renal failure, and proteinuria have yielded encouraging results with respect to reduction of proteinuria and stabilization of renal function (83,89,90). The mechanism(s) whereby ACE inhibitors might benefit these patients are still unclear and may include hemodynamic factors, decreasing expression of renal growth factors and cytokines, or even affecting HIV protease activity (83,90).

At present, the therapy of HIV-associated nephropathy remains controversial. From a number of studies, it appears that early diagnosis and biopsy documentation of the lesion of HIV-associated nephropathy is important in influencing the institution and choice of therapy. Treatment with antiretroviral medication(s) appears warranted, although the agents used, the indications for combination therapy, and specific regimens will require controlled trials to define. Use of ACE inhibition early in the disease, with careful attention to hyperkalemia, renal dysfunction, and episodes of volume depletion (which can be associated with hyperkalemia and azotemia), appears beneficial. Again, the exact dose and type of therapy remains to be defined. Clearly the use of immunosuppressive medications, whether corticosteroids or cyclosporine, has the potential for significant harm in this population. These agents should be considered experimental until further studies have clarified their therapeutic role.

Dialysis. Hemodialysis. There has been great concern regarding optimal mode of dialysis replacement therapy in HIV-infected patients, and the potential spread of HIV to staff and hospital workers. Until recently, most dialysis centers were not routinely testing patients for HIV status. Many, however, recommended testing high-risk patients. The incidence of HIV seropositivity in a given dialysis unit depends upon the population served. In national surveys of dialysis populations, only a fraction of a percentage of patients will be seropositive (92). However, in one inner-city unit, 38% of the patients were HIV-positive. Although initial studies found a low survival rate in hemodialyzed HIV-infected patients, recent studies segregating the patients by the stage of the HIV infection have found better results (21). A recent study from New York found a 1-yr survival rate of 16% for dialysis patients with AIDS versus a 77% survival rate for HIV-seropositive patients without AIDS (22). Likewise, another New York study found that of 160 HIV-positive patients hemodialyzed over an 8-yr period, 115 had HIV nephropathy, whereas 45 had other causes of ESRD (24). Patients with HIV-associated nephropathy had a shorter survival from onset of renal disease (14 versus 93 months) and from time of ESRD to death (8.7 versus 34 months). However, there was no difference in survival between these groups from first manifestation of HIV infection, AIDS-related complex, or AIDS until death. These studies confirm our original observation that the status of the HIV infection is the major determinant of survival in patients with HIV nephropathy (8). Although there have been only a few long-term survivors on dialysis with AIDS, many centers have had patients survive for several years with asymptomatic HIV infection and HIV nephropathy. In a study from Miami, the mean survival for hemodialysis patients with AIDS was 93 days, whereas the mean survival for asymptomatic HIV carriers was 488 days (range, 150 to 1230 days) (93). At present, AIDS is a major cause of mortality in the inner-city dialysis population (43).

Although there was considerable initial fear among the nephrology community of possible transmission of HIV in the dialysis setting, such concerns have been eased by increasing awareness of the low rate of infectivity of HIV in the nosocomial setting (93). The Centers for Disease Control and Prevention concluded that HIV is far less contagious than hepatitis B, and that measures of dialysis machine sterilization and infection control routinely utilized to prevent hepatitis B transmission are adequate to minimize the risk of HIV transmission (93). To date, there are no reports of transmission of HIV to patients or dialysis staff member in the United States as a direct result of dialysis treatment (21,94–96). A widely publicized
study of an epidemic among dialysis patients in a dialysis unit in Columbia, South America was investigated by the Centers for Disease Control and Prevention (33,94). Patient-to-patient spread was documented from cross-contamination of reprocessed, inadequately disinfected access needles (a practice common in some countries, but not in the United States). The lack of such an occurrence in the United States attests to both the low risk of transmission and the adequacy of current dialysis control measures.

**Peritoneal Dialysis.** Peritoneal dialysis has been used in HIV-infected patients with mixed results (21). In general, HIV patients have a shorter survival than noninfected patients (21,97,98). Survival, as in hemodialysis patients, correlates with the stage of the HIV infection (89,91). Rates of peritonitis have been found to be higher than in control populations in some series, but not in others (21,97,98). Despite its drawbacks, peritoneal dialysis and continuous ambulatory peritoneal dialysis are reasonable options for some HIV-infected patients with ESRD.

**Transplantation.** It is well recognized that donor organs are a potential source of HIV transmission to the recipient. Cadaver renal transplants have been reported to be a source of HIV transmission in some patients (21,99,100). Thus, HIV screening is mandatory for all potential kidney donors. In addition, regardless of HIV serologic testing, all patients from certain high-risk groups, such as IVDA and hemophiliacs, are categorically excluded from the donor pool. Controversy exists regarding the feasibility, risk, and cost-effectiveness of transplantation in HIV-infected patients with ESRD as a result of HIV nephropathy or unrelated diseases (21,100). Whereas most centers will not perform renal transplants in this population, not all centers agree, and some renal transplants have been performed—knowingly or unknowingly—in HIV-infected patients (100,101). Some of these renal transplant recipients are alive with functioning grafts for over 5 yr after transplantation. Several renal transplant recipients who contracted HIV as a consequence of undiagnosed HIV infection in the donor have died as early as 5 months after transplantation as a result of infectious complications of AIDS (21,101). Recognition of the development of HIV infection after renal transplantation requires an awareness of which opportunistic infections occur in the transplant recipient, and knowledge of the timing and severity of such infections (99).

**Other Glomerular Lesions**

The incidence of reported immune-complex glomerulonephritis among HIV-infected individuals in different geographic locales varies according to the demographics of the biopsy population. Although classic HIV-associated nephropathy of the focal sclerosis type continues to predominate in the urban centers of New York and Miami, higher rates of immune complex mediated disease have been reported in Washington, D.C., Paris, and Italy (39,50,105). A multicenter Paris-based study of HIV-infected patients, including 29 blacks from Africa, Haiti, and the West Indies and 31 White Europeans, found immune-complex forms of glomerulonephritis in 52% of whites but only 21% of blacks (39). Biopsies from 26 white HIV-infected adults in Northern Italy revealed a variety of glomerular lesions, most of which were immune-complex-mediated, but no case of classic HIV-associated nephropathy (105). In our own experience, MPGN (either Type 1 or 3) is common and usually associated with hepatitis C coinfection (Table 1). Lupus-like nephritis with high-titer ANA, anti-DNA antibody, and hypocomplementemia has also been reported in HIV-infected patients, particularly children (13,39,106,107).

Few investigators have attempted to determine the composition and specificity of the glomerular immune deposits. In one study of four patients with immune-complex-mediated glomerulonephritis, viral antigen was detected in the glomeruli by direct immunofluorescence, and antibodies eluted from the kidney reacted with HIV antigens present in the circulating immune complexes (CIC) (50). These CIC consisted of IgA-p24 HIV antigen in one patient, IgG-p24 HIV antigen in two patients and IgG-gp120 HIV antigen in the fourth. Antibody from the CIC of each patient also reacted in an immunodiffusion assay with antigen eluted from the renal biopsies. These finding strongly suggest that, in some individuals, proliferative glomerulonephritis may result from renal deposition of preformed CIC with specificity for HIV core or envelope proteins.

IgA nephropathy in association with HIV infection has been reported with increasing frequency (108-110). Two cases were characterized by hypocomplementemia and elevated serum IgA levels with CIC containing IgA idiotypic antibodies (110). In one patient, an IgA cryoglobulin was reactive with whole IgG directed against HIV gp41. The other case lacked identifiable cryoglobulin but contained an IgA idiotypic antibody reactive with whole IgM possessing anti-HIV p24 activity. The observation that the IgA class of immunoglobulins is typically the most elevated in HIV patients with polyclonal gammapathy may predispose to the development of IgA nephropathy through altered immune regulation in response to continuous production of anti-HIV antibodies (111).

In recent years there have been increasing reports of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in HIV-infected patients (112). At least 18 cases have been reported, with a median age of 32 (range, 25 to 52 yr). Fifty percent of patients were homosexual, and 89% were male. Cases occurred at all stages of HIV infection, although most (50%) had late-stage disease. Hematuria and proteinuria were present in 90% and 80% of cases, respectively, and serum creatinine concentrations ranged from 0.8 to 4.8 mg/dL. Twenty-eight percent of patients died of their HUS/TTP, whereas 50% responded to conventional therapy including plasma exchange, fresh-frozen plasma, corticosteroids, or anti-platelet agents. The cause of HUS in the HIV-infected population is unknown. There is no clear association with *Escherichia coli* 0157:H7 infection, and intercurrent infections have been demonstrated in only one third of patients. Potential roles for direct or indirect endothelial injury by HIV virus (113) or direct viral infection of platelet-precursor cells with resulting cytopathic effects (114) have been proposed.

**Summary and Conclusions**

HIV-infected patients may present with a variety of patterns of renal involvement. Acute renal failure is common and most often a result of sepsis, hypotension, and nephrotoxic agents. It
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is potentially avoidable, and support through the period of renal failure may lead to resolution of the renal dysfunction. HIV-associated nephropathy is a unique pattern of sclerosing glomerulopathy that ranges in prevalence from 1 to 10% of the HIV-infected population in different geographic locales. This complication of HIV infection will likely present a growing challenge to the medical community as HIV infection continues to spread worldwide. Deciphering the pathogenetic mechanisms of this most rapidly progressive form of focal segmental sclerosis is not only clinically relevant, but will hopefully provide valuable insights into the mediation of the more common idiopathic form of the disease. The potential for improved renal survival of patients with HIV-associated nephropathy has become more realistic with the development and use of anti-retroviral agents, as well as studies on the role of immunosuppression and ACE inhibition in this population. An awareness of other glomerular lesion and tubulointerstitial lesions has broadened our understanding of populations with renal disease who have been infected by HIV. Moreover, as prolonged survival of HIV-infected individuals is being achieved with modern antiviral therapy, the percentage of patients surviving with nephropathy will likely grow in coming years. Awareness of the growth of this population and those requiring short- and long-term hemodialysis and peritoneal dialysis will allow appropriate planning for ESRD in the HIV-infected population.

References

104. Itescu S, Rose S, Dwyer E, Winchester R: Certain HLA-DR5 and -DR6 major histocompatability complex class II alleles are associated with a CD8 lymphocytic host response to human immunodeficiency virus type I characterized by low lymphocyte viral strain heterogeneity and slow disease progression. Proc Natl Acad Sci USA 91: 11472–11476, 1994


