REVIEW

HIV-1 Infection and the Kidney: An Evolving Challenge in HIV Medicine

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With the advent of highly active antiretroviral therapy (HAART), the incidence of opportunistic infections has declined substantially, and cardiovascular, liver, and renal diseases have emerged as major causes of morbidity and mortality in individuals with human immunodeficiency virus (HIV). Acute renal failure is common in HIV-infected patients and is associated with acute infection and medication-related nephrotoxicity. HIV-associated nephropathy is the most common cause of chronic kidney disease in HIV-positive African American populations and may respond to HAART. Other important HIV-associated renal diseases include HIV immune complex kidney diseases and thrombotic microangiopathy. The increasing importance of non–HIV-associated diseases, such as diabetes mellitus, hypertension, and vascular disease, to the burden of chronic kidney disease has been recognized, focusing attention on prevention and control of these diseases in HIV-positive individuals. HIV-positive individuals who experience progression to end-stage renal disease and who have undetectable HIV-1 viral loads while receiving HAART should be evaluated for renal transplant. Emerging evidence suggests that HIV-positive individuals may have graft and patient survival comparable to HIV-negative individuals. Several studies suggest that HIV-1 can potentially infect renal cells, and HIV transgenic mice have clarified the roles of a number of HIV proteins in the pathogenesis of HIV-associated renal disease. Host factors may modify disease expression at the level of cytokine networks and the renal microvasculature and contribute to the pathogenic effects of HIV-1 infection on the kidney.

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ACE = angiotensin-converting enzyme; ARF = acute renal failure; CKD = chronic kidney disease; CMV = cytomegalovirus; ESRD = end-stage renal disease; FGF = fibroblast growth factor; FGS = focal segmental glomerulosclerosis; GFR = glomerular filtration rate; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; HIVAN = HIV-associated nephropathy; HIVMA-IDSA = HIV Medicine Association of the Infectious Diseases Society of America; HIVICK = HIV immune complex disease; IL = interleukin; IRS = indinavir renal syndrome; OI = opportunistic infection; PI = protease inhibitor; TGF-β = transforming growth factor β; TMA = thrombotic microangiopathy

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Major advances in human immunodeficiency virus (HIV) care have resulted in improved survival and a decreased incidence of opportunistic infections (OIs) for individuals receiving highly active antiretroviral therapy (HAART).[1] The causes of mortality in HIV-1–positive individuals have changed, and cardiovascular disease, hepatic failure, and end-stage renal disease (ESRD) have emerged as challenging problems.[2] Renal disease was first reported in HIV-1–seropositive individuals in 1984, and initial reports identified both focal segmental glomerulosclerosis (FGS) and other renal diseases.[3,4] HAART has altered the spectrum of renal diseases encountered in HIV-positive individuals: whereas the incidence of HIV-associated nephropathy (HIVAN) has declined in the HAART era,[5] the burden of chronic renal disease due to diabetes mellitus, hypertension, and nephrotoxicity associated with antiretroviral therapy has increased. The increased life expectancy of HIV-infected patients with chronic kidney disease (CKD) has resulted in an increasing number of HIV-positive individuals with ESRD.[6] The management and prevention of CKD in HIV-positive individuals have emerged as major medical challenges.

In this review, we describe the spectrum of acute and chronic renal disease associated with HIV infection and summarize current etiologic, diagnostic, and therapeutic considerations for these clinical entities. In addition, we review state-of-the-art scientific literature regarding the direct pathophysiological effects of HIV and its molecular components on resident and infiltrating cells within the kidney.

ACUTE RENAL FAILURE

The AIDS Clinical Trials Group has defined acute renal failure (ARF) in HIV-seropositive patients as a creatinine level greater than 1.5 mg/dL or a 1.3-fold increase above laboratory baseline that resolves within 3 months. This definition has been included in recent guidelines from the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA-IDSA).[7] Although prerenal azotemia and acute renal injury from drug toxicity associated with the treatment of OIs or AIDS-related malignancy are major causes of ARF, case series and reviews have also noted other causes, including HIV thrombotic

microangiopathy (TMA) and statin-associated rhabdomyolysis.[8-10] Both TMA- and rhabdomyolysis-induced ARF have also been described in case reports as presenting features of primary HIV infection.[11-15] HIV-positive individuals have an increased risk of developing ARF while hospitalized, and ARF is associated with increased mortality.[16] The adjusted odds ratio for ARF in HIV-positive individuals was elevated in both the pre-HAART (4.6) and post-HAART (2.8) eras.

Pre-HAART ARF was associated with younger age, OIs, and septicemia.[17] The rate of renal recovery and mortality in those given renal replacement therapy was similar to HIV-negative individuals, but HIV-positive individuals who were more ill did not undergo dialysis. During *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) infection, ARF occurred because of clumps of organisms obstructing glomerular and intertubular capillaries and resulted in the appearance of renal calcification on computed tomography.[18,19] Although rarely observed in clinical practice, several different microsporidia have been implicated as a cause of ARF, with reports of improvement with albendazole.[20-23] Viral mechanisms of ARF included tubulointerstitial nephritis secondary to Epstein-Barr virus, cytomegalovirus (CMV), or BK virus and an isolated case of CMV ureteritis in a HIV-infected child.[24-27] Other associations have included cortical abscesses secondary to *Cryptococcus* and *Nocardia* species, granulomatous nephritis secondary to tuberculosis and atypical mycobacterial infection, and less commonly renal mycotic infections due to histoplasmosis, aspergillosis, and zygomycosis.[24,28-33] Acute interstitial nephritis secondary to immune restoration inflammatory syndrome after initiation of HAART has also been reported.[34]

In an ambulatory HIV-positive population that attended a single infectious disease clinic in North Carolina, ARF incidence was 5.9 per 100 person-years in the post-HAART era.[9] The most common mechanisms of ARF were prerenal in 38% of cases (most frequently due to dehydration, sepsis, or liver disease) and acute tubular necrosis in 48% (mainly ischemic or nephrotoxic). Less common causes included interstitial nephritis and obstructive nephropathy. Risk factors for ARF included male sex, CD4 cell count less than 200/μL, HIV RNA level greater than 10,000 copies/mL, having ever received HAART, and hepatitis C coinfection.[9] In the post-HAART era, ARF is more likely to be associated with traditional non–HIV-associated risk factors, such as older age, diabetes mellitus, chronic renal diseases, and liver failure.[16]

False-positive antibodies to antineutrophil cytoplasmic antibodies and anti–glomerular basement membrane antibodies are a feature of HIV infection and must be interpreted cautiously during HIV-associated ARF.[35,36]

CHRONIC KIDNEY DISEASE

The HIVMA-IDSA guidelines on HIV-related renal disease recommend use of the term *chronic kidney disease* as defined by the National Kidney Foundation,[7] which refers to documented kidney damage present for 3 months or more and graded by calculating either the creatinine clearance using the modified Cockcroft-Gault equation or the glomerular filtration rate (GFR) by use of the modification of diet in the renal disease equation.[37] The guidelines also stress the importance of measuring "spot" urinary albumin and/or protein to creatinine ratios to screen for early CKD.[7]

The incidence of CKD during HIV infection is difficult to estimate. Rates are highest in African American males in whom HIVAN represents the third leading cause of CKD.[38-40] Cohort studies suggest that approximately 30% of HIV-positive individuals have proteinuria (≥1+),[41] whereas a large Centers for Disease Control and Prevention–sponsored Women's Interagency HIV Study found that 7.2% of HIV-positive women had proteinuria (2+) at baseline, with a further 14% developing proteinuria (2+) during the median follow-up period of 21 months.[42] Single estimates suggest that 19% to 30% of HIV-positive individuals have microalbuminuria,[43,44] whereas 6% of this population has overt proteinuria.[44]

Chronic kidney disease is associated with increased progression to AIDS and death, even after HAART.[45] Individuals with CKD are more likely to experience drug adverse effects with protease inhibitors (PIs).[46] Anemia is more marked in HIV-associated ESRD.[47,48] However, the efficacy of recombinant human erythropoietin therapy in treating anemia appears comparable between HIV-associated and HIV-independent ESRD.[47] Patients with HIV infection may require higher doses of erythropoietin because of lower baseline hematocrits than their HIV-negative counterparts.[49] Also, HIV-positive individuals may have an increased risk of renal osteodystrophy because HIV infection and its treatment have been associated with loss of bone mineral density.[50] HIV-positive individuals have lower parathyroid hormone and vitamin D levels.[48,51] In our own cohort of HIV-positive persons, we have confirmed prior findings that vitamin D deficiency is associated with lower CD4 T-cell counts[52] and also demonstrated an association with African race (T.I.d.S., D.H.D, unpublished data, 2005). HIV-positive individuals with ESRD have an increased risk of cardiovascular disease, which is likely to result from dyslipidemia associated with HAART and (proteinuric) renal disease.[53,54]

HIV-Associated Nephropathy

HIV-associated nephropathy is the most common cause of CKD in HIV-positive persons,[39] accounting for approxi-

mately half of cases in 6 US medical centers.[45] It is characteristically a disease in those of African descent and is less common in Asian populations.[8,55-57] HIV-associated nephropathy is characterized by proteinuria, absence of edema, renal failure, and large echogenic kidneys apparent on ultrasonography.[8,58,59] Although severe proteinuria may be usual in most patients who present with HIVAN, a wide variation in values is seen.[58,60] In one South African series, although the mean protein level in biopsy-proven cases of HIVAN was 11.8 g/d, the range observed was 1.7 to 40 g/d,[60] whereas another study reported values as low as 0.06 g/d.[58] An increased incidence of pelvocalyceal thickening apparent on ultrasonography was also noted in one study.[61] Individuals are frequently normotensive, which is unusual given the increased incidence of hypertension among black patients.[62]

The classic pathological findings are of FGS with focal or global collapsed glomeruli, mesangial hyperplasia with increased cellularity, and mesangial matrix deposition.[63] Tubular interstitial inflammation can be prominent and more marked than anticipated for the degree of glomerular injury. Microtubular cystic dilation, a feature that helps distinguish HIVAN from idiopathic collapsing glomerulopathy, is usually prominent and may be directly related to HIV-1 infection of renal epithelial cells.[64] Electron microscopy may reveal tubuloreticular structures in glomerular endothelial cells, which have also been described in lupus nephritis.[65,66] Immunofluorescence microscopy findings are negative or nonspecific.

Classically, HIVAN was described as a late manifestation of HIV infection, associated with low CD4 cell counts and high viral loads, although it has been described both as part of an acute retroviral syndrome[67-69] and in a patient receiving HAART with an undetectable viral load in blood and renal tissue.[70] Familial clustering of cases in African American populations and in families with a history of other non–HIV-associated renal diseases suggests that a genetic element exists.[40] To date, however, the main genetic association identified has been with an angiotensin-converting enzyme (ACE) polymorphism associated with both HIVAN and idiopathic FGS.[71] Evidence exists for direct viral effects on the kidney in HIVAN pathogenesis since HAART appears to slow the decline in renal function in patients diagnosed as having HIVAN,[45,72] and several different HIV transgenic models of HIVAN suggest an effect of HIV gene products on the initiation of disease.[73-79] Further support is provided by the observation that relapse of HIVAN can occur after cessation of HAART.[80] Additional host factors are likely to modify disease phenotype because renal replication of HIV may occur in most individuals but only a subset develop proteinuria and CKD.[8] Transforming growth factor β (TGF-β) levels are increased in the kidneys of individuals with HIVAN,[81] and since the angiotensin-renin system has been demonstrated to drive TGF-β gene expression in a rat model,[82] this observation links with data on polymorphism of the *ACE* gene.

Diagnosis of HIVAN requires a biopsy, and noninvasive diagnostic techniques have been disappointing.[72,83] Detectable viremia is usually a feature at HIVAN presentation.[45] Patients with HIVAN may experience rapid progression to ESRD.[59,84] HAART delays progression to ESRD with an adjusted hazard ratio for renal survival of 0.30 (95% confidence interval, 0.09-0.98),[72] although a proportion of patients will still require renal replacement therapy despite HAART.[45] The incidence of HIVAN has decreased considerably in the HAART era, with risk reductions of approximately 60% in a multivariate analysis.[5] Protease inhibitors have been linked to delayed progression,[85] although it is unclear whether these benefits reflect unique intrinsic properties of the drugs[86] or the greater viral suppression of PI-containing HAART compared with earlier monotherapy or dual therapy. Direct beneficial effects of PIs on HIV-related kidney disease may include inhibition of apoptosis and superoxide generation, interference with the production and release of inflammatory cytokines and chemokines, and down-regulation of endothelial cell expression of adhesion molecules crucial in mediating leukocyte recruitment to sites of inflammation.[86-88] In patients with progression despite HAART, corticosteroids are recommended[7] on the basis of retrospective and prospective studies showing benefit.[85,89] One prospective, open-label study in patients receiving monotherapy or dual antiretroviral therapy showed a decrease in serum creatinine levels (mean decrease, 8.1-3.0 mg/dL) and 24-hour urinary protein excretion (mean decrease, 9.1-3.2 g/d) with glucocorticoid therapy,[89] and infectious complications were infrequent. Data on the use of other immunosuppressants are scarce, although one small case series demonstrated improved renal function in patients with HIVAN after administration of cyclosporine.[90]

In a multicenter, retrospective study, ACE inhibitors or angiotensin receptor blockers delayed the time to renal replacement.[45] In a single-center, nonrandomized prospective series, patients with biopsy-proven HIVAN were given either fosinopril, 10 mg/d, or no ACE inhibitors before the onset of severe renal insufficiency (serum creatinine level ≤2.0 mg/dL) and were followed up for 5.1 years.[91] Multivariate analysis revealed a reduced risk of renal failure, greater overall survival, improved creatinine levels, and stabilization of proteinuria associated with fosinopril, with no difference in exposure to antiretroviral therapy between the 2 groups. Current guidelines reserve ACE inhibitor use to the subset of individuals with hypertension and proteinuria, with the goal of keeping blood pressure less than 125/75 mm Hg, in line with the recommendations for HIV-negative CKD.[7]

TABLE 1. **Potential Causes of Chronic Kidney Disease in HIV-Infected Individuals and Reported Associated Conditions***

Condition	Associations
HIV-associated nephropathy[39]	
HIV immune complex disease[8,44,56,60]	
Immune complex–mediated GN[8]	
IgA nephritis[56,60,92]	
Postinfectious GN[60]	
Membranous nephritis[60]	HBV, HCV, syphilis, SLE[45,93,94-97]
Membranoproliferative GN[60]	HBV, HCV, and/or mixed cryoglobulinemia[93,94]
Mesangial proliferative GN[93]	HCV[93]
Fibrillary or immunotactoid GN[98]	HCV[99]
Mixed inflammatory or sclerotic variant[56]	
Lupus-like nephritis[56,100]	
Interstitial nephritis[56,60]	Drugs, cytomegalovirus, EBV, BK virus, *Cryptococcus neoformans* tuberculosis, adenovirus[26,57,101-105]
Thrombotic microangiopathies[106,107]	
Minimal change glomerulonephritis[8]	
Diabetic nephropathy[108]	
Hypertensive nephropathy[108]	

*EBV = Epstein-Barr virus; GN = glomerulonephritis; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus.

Non-HIVAN Causes of CKD

In a US series, the most common non-HIVAN causes of glomerular disease were HIV immune complex disease (HIVICK), membranous nephropathy, membranoproliferative glomerulonephritis, and diabetic glomerulopathy.[45] In a South African biopsy series, HIVICK and membranous nephropathy were most common, followed by postinfectious glomerulonephritis and IgA nephropathy.[60] Non-HIVAN causes of CKD are more likely to occur in individuals who are not black, are normotensive, are hepatitis B coinfected, and have higher CD4 cell counts.[45]

HIV Immune Complex Disease

HIV immune complex disease represents a variety of histological entities (Table 1). In contrast to HIVAN, in which the renal infiltrate is composed of T lymphocytes and macrophages, in HIVICK it consists of B lymphocytes.[109] The pathogenesis of the different forms of HIVICK may have common etiologic features, including deposited immune complexes containing HIV-1 antigens, characteristic cytokine expression profiles, genetic factors, inflammatory infiltrates, and the development of renal scarring.[106]

IgA nephropathy was shown to occur in 8% of individuals in one postmortem series[92] and is believed to be the result of immune complexes that contain HIV antigens.[44] It presents with proteinuria, hematuria, and mild renal impairment and is less severe than HIVAN and some other variants of HIVICK.[8] However, in the South African series referred to previously, IgA nephropathy led to severe renal impairment and proteinuria.[60] Elevated levels of serum IgA, as well as detectable serum IgA immune complexes and rheumatoid factor, may be present.[110]

Lupus-like nephropathy typically presents with microscopic hematuria, proteinuria, and renal impairment, with relatively rapid progression to renal failure.[100] Histological analysis can show diffuse or focal proliferative changes, sometimes shows membranous nephropathy, and frequently shows crescent formation and tubulointerstitial scarring.[100] An unusual feature is large subepithelial deposits with a basement membrane reaction that consists of a ball-in-cup pattern.[60] Lupus-like nephropathy may be more common in men of African descent and typically occurs in the absence of significant serologic positivity for lupus.[100] The optimal management of these conditions remains unclear, with case reports of benefits from ACE inhibitors, corticosteroids, and HAART[106] but some series have failed to show that HAART influenced the progression to ESRD.[45]

HIV Thrombotic Microangiopathy

HIV-associated TMA takes 2 classic forms: hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.[8] Pathological findings are similar in both forms, with fibrin-rich thrombi and platelets deposited in the glomerular capillaries and arterial microvessels.[106] Intimal edema, fibrinoid necrosis, microcystic tubular lesions, and onion skin lesions are a feature, as in HIV-negative TMA. HIV-associated TMA predominantly affects white populations,[106] and apart from one series in which most cases occurred in women, TMA tends to affect children and young males.[107] Compared with HIVAN, TMA is rare, but HIV-related TMA may account for up to 35% of all TMA cases.[111,112] Microangiopathic anemia and renal impairment predominate in hemolytic uremic syndrome, whereas in thrombotic thrombocytopenic purpura a pentad of microangiopathic

anemia, thrombocytopenia, renal impairment, fever, and neurologic features occurs. Proteinuria can be in the nephrotic range but is usually less marked than in HIVAN.[113] Typically, TMA is a feature of chronic HIV infection but, as aforementioned, can occur during acute retroviral syndrome.[15] A case-control study noted endothelial CMV inclusion in a subset of biopsy specimens from HIV-associated TMA, but whether CMV contributes to pathogenesis remains unclear.[114]

Treatment is plasma infusion and plasmapheresis, whereas splenectomy is reserved for refractory disease.[8] One series from South Africa suggested that HIV-positive patients were more responsive to plasma infusion with fresh frozen plasma than HIV-negative patients and less likely to require plasma exchange.[107] Moreover, in HIV-positive patients, the time for platelet counts to increase and lactate dehydrogenase to normalize was shorter. Reports of responses to antiretroviral therapy exist, as does anecdotal experience with antiplatelet agents, corticosteroids, and vincristine.[8] Mortality exceeds 60% in HIV-associated TMA.[106]

TABLE 2. **Examples of Renal Injury Caused by Drugs Used to Treat Opportunistic Infections in Human Immunodeficiency Virus–Positive Patients**

Type of renal injury	Drug
Acute tubular necrosis	Pentamidine[115] Foscarnet[116-118] Cidofovir[119] Adefovir[119] Amphotericin B[120,121] Aminoglycosides[120] Trimethoprim-sulfamethoxazole[118,122]
Intratubular obstruction secondary to crystal precipitation	Sulfadiazine[123,124] Foscarnet[125] Acyclovir[126,127]
Interstitial nephritis[101,128,129]	β-Lactam antibiotics Quinolones Trimethoprim-sulfamethoxazole Rifampicin
Crescenteric glomerulonephritis	Foscarnet[130] Rifampicin[131]
Nephrogenic diabetes insipidus	Foscarnet[132,133]
Renal tubular acidosis	Trimethoprim-sulfamethoxazole (trimethoprim component)[134-136] Foscarnet[133]

DRUG-RELATED RENAL INJURY

Many drugs used in the treatment or prophylaxis of OIs in HIV infection may cause nephrotoxicity (Table 2). The potential renal effects of trimethoprim-sulfamethoxazole are worth mentioning, specifically because it is frequently used in HIV-infected individuals both in the treatment of and as primary or secondary prophylaxis of a variety of OIs. Acute tubular necrosis and acute interstitial nephritis can both occur, and the latter may respond to corticosteroid therapy.[118,122,137,138] Severe hyperkalemia is a recognized consequence with both high- and standard-dose trimethoprim-sulfamethoxazole, and it is attributed to reduced renal potassium excretion through competitive inhibition of epithelial sodium channels in the distal nephron, in a manner similar to the action of potassium-sparing diuretics such as amiloride.[139,140] Acute metabolic acidosis is also reported and presumed to be a renal tubular acidosis in origin.[134-136] Of note, trimethoprim can increase serum creatinine levels by altering normal elimination pathways, with no evidence of deterioration in GFR.[141,142] Although rare cases of renal insufficiency due to ritonavir and recent case reports of efavirenzand atazanavir-induced nephrolithiasis and abacavir-induced tubular dysfunction exist, 2 antiretrovirals account for most antiretroviral-related cases of renal disease.[143-147]

TENOFOVIR

The nucleotide analogues cidofovir and adefovir are associated with nephrotoxicity. Although ARF in association with the nucleotide analogue tenofovir has been reported,[148] whether tenofovir therapy has long-term renal effects is less clear. In vitro studies suggest little toxicity.[149] A renal biopsy series suggested that the mitochondrial to nuclear DNA ratio was unchanged in HIV-positive individuals who received tenofovir compared with those who did not, although the combination of tenofovir with didanosine was associated with a reduced ratio.[150] Individuals who received tenofovir had increased ultrastructural mitochondrial abnormalities. A large cohort study demonstrated a minimal, albeit statistically significant, reduction in estimated creatinine clearance and an increased anion gap in individuals receiving tenofovir in the first 1.7 years of treatment.[151] The duration of therapy was not significant in multivariate analysis. Further studies have shown only minimal decreases in the GFR of individuals taking tenofovir and a low incidence (0.3%) of ARF.[152,153] Intercurrent illnesses and coadministered drugs (including didanosine) may have contributed to ARF in these studies.[151] Competition between tenofovir and didanosine for active uptake into proximal renal tubular cells, a process controlled by the human organic anion transporter 1,[154] could facilitate greater didanosine serum concentrations and therefore mitochondrial damage and nephrotoxicity during coadministration without dose adjustment of didanosine.[148]

The observation that 93% of tenofovir-associated renal impairment occurred in individuals taking PIs has led to speculation that ritonavir-mediated inhibition of the multidrug resistance protein 2, which secretes tenofovir into the urine, might lead to intracellular accumulation of the drug.[148] Others have argued that multidrug resistance

protein 4, not multidrug resistance protein 2, mediates tenofovir efflux and is not inhibited by ritonavir.[151,155] A population-based pharmacokinetic study demonstrated that the combination of lopinavir and ritonavir decreases tenofovir clearance,[156] but by multivariate analysis concomitant lopinavir-ritonavir use is not associated with an increase in the serum creatinine level.[153] The association with PIs may reflect greater PI use and greater renal impairment in individuals with lower CD4 cell counts.

Another adverse effect of tenofovir is the development of Fanconi syndrome with phosphate wastage along with loss of potassium, bicarbonate, uric acid, amino acids, and glucose in the urine.[157,158] As with ARF, most cases have occurred in association with concomitant PI use. Another small study suggested that, although overt phosphate depletion and renal impairment were rare in individuals taking tenofovir, decreased reabsorption of phosphate and high urinary β_2-microglobulin levels were observed in 70% of individuals receiving tenofovir.[159] However, one study suggested that hypophosphatemia and decreased phosphate reabsorption were common in HIV-positive individuals before tenofovir treatment and remained stable with tenofovir treatment.[160]

During 3 years of follow-up, although minor laboratory abnormalities occurred with tenofovir, overt renal failure was rare and usually explicable by other factors.[154,161] Furthermore, the reported episodes of proximal renal tubule dysfunction were reversible with discontinuation of tenofovir therapy.[162] The HIVMA-IDSA guidelines recommend that individuals who receive tenofovir and have diabetes mellitus and/or hypertension, have a GFR less than 90 mL/min per 1.73 m^2, and receive medications with renal secretion or boosted PIs should undergo biannual renal function and serum phosphorus testing and urinalysis.[7]

Indinavir

Indinavir crystalluria occurs in 20% or less of individuals receiving indinavir.[81] Presentations of indinavir renal syndrome (IRS) include ARF, asymptomatic crystalluria, symptomatic crystalluria with flank pain and dysuria, nephrolithiasis, and chronic renal impairment with tubulointerstitial injury.[163-166] In nephrolithiasis, imaging studies will reveal secondary signs of obstruction with no calculi because indinavir stones are radiolucent.[167] A retrospective cohort study identified an incidence of indinavir-associated nephrotoxicity of 6.7 per 100 person-years of indinavir use.[165] Fluid deprivation, alteration of indinavir dose, and acyclovir coadministration are cofactors in IRS. Insidious renal impairment develops with tubular crystals, tubule necrosis, and dilation, with diffuse eosinophilic interstitial infiltrates and scarring.[166] Leukocyturia is common and persistent in 32% of individuals taking indinavir.[168]

When IRS is defined as an elevation in the creatinine level of 20% or more above baseline, the likelihood of IRS increases with time, suggesting that this manifestation is more chronic, unlike the more acute syndrome aforementioned.[169] Defined as such, IRS was documented in 18.6% of a cohort and was associated with low baseline body mass index, concomitant trimethoprim-sulfamethoxazole use, and the presence of chronic viral hepatitis.[170,171] The HIVMA-IDSA guidelines recommend that individuals receiving indinavir should drink at least 1.5 L of water per day and that periodic monitoring of creatinine and urinalysis for pyuria be performed in the first 6 months of treatment.[7] For those in whom nephrolithiasis develops, indinavir therapy can be resumed after treatment of the nephrolithiasis, unless an elevated creatinine level, pyuria, hypertension, or rhabdomyolysis is present.

Dose Adjustment of Renal Medications for Individuals With CKD

Dose adjustments required for medications commonly used in HIV treatment are summarized in the HIVMA-IDSA guidelines.[7] Although data for many of these recommendations are limited, in general PIs and nonnucleoside reverse transcriptase inhibitors do not require dose adjustment in patients with renal impairment, whereas most nucleoside analogues (except abacavir) do.[7,172] Data for newer antiretrovirals are scarce, although the fusion inhibitor enfurvitide may not require dose adjustment.[173]

RENAL REPLACEMENT IN HIV-INFECTED INDIVIDUALS

Survival of HIV-positive individuals with ESRD, which formerly lagged behind the rates for HIV-negative individuals, is now similar, with 1-year survival rates of 74%.[174] The HIVMA-IDSA guidelines emphasize the importance of controlling hypertension, and aggressive management of cardiovascular risk factors is an increasingly important aspect of both HIV care and the management of CKD.[7,53] Access for hemodialysis is best provided by a native arteriovenous fistula, which provides superior fistula patency and lower rates of infection.[175] Hemodialysis-induced cytokine stimulation does not increase HIV-1 replication.[176,177] Although less often used, continuous ambulatory peritoneal dialysis is used successfully in HIV-positive individuals.[178] Studies from the pre-HAART era identified increased infections (particularly from *Pseudomonas aeruginosa* and fungi) during continuous ambulatory peritoneal dialysis.[179] Since the advent of HAART, a survival time of up to 12.5 years has been demonstrated with continuous ambulatory peritoneal dialysis, although with significantly greater rates of hospitalization and peritonitis in HIV-positive individuals.[180]

Transplant Surgery

Until relatively recently, renal transplant was rarely performed in HIV-positive individuals. Allograft recipients were shown to have more rapid progression to AIDS[181] and significantly lower patient and graft survival.[182] In the HAART era, a number of small series have emphasized the improved outcomes with renal transplant, with graft survival and patient survival approximating those in HIV-negative populations.[183-185] Such improvement now makes renal transplant a realistic option,[186] and HIV-positive renal allograft recipients have better 2-year survival rates than do HIV-positive individuals who continue to undergo dialysis, although selection bias may influence these figures.[184] Although confirmation of the feasibility and clinical benefit of renal allografts in HIV-positive patients has resulted in broad acceptance of both living and deceased donor transplant in this population, significant challenges to successful transplant outcomes remain.[187] Transplant in HIV-positive individuals is associated with higher serum creatinine levels and a greater incidence of rejection.[188,189] Short-term rejection has been reported in 40% to 70% of HIV-positive recipients of renal allografts, representing more than a doubling of the rejection rate compared with HIV-negative recipients. Furthermore, corticosteroid-resistant rejection is relatively more common, necessitating therapy with T-cell–depleting antibody preparations with associated prolonged $CD4^+$ T-cell deficiency and increased risk of severe infection.[190] Protease inhibitors significantly increase serum levels of the calcineurin inhibitor immunosuppressants (cyclosporine and tacrolimus) and the mammalian target of rapamycin inhibitor sirolimus, whereas nonnucleoside reverse transcriptase inhibitors may reduce levels to a modest extent.[162,191] Thus, the risk for both immunosuppression-related toxicity and inadequate antirejection therapy is exaggerated in allograft recipients receiving HAART. However, concerns that these interactions might increase HIV-1 viral loads have been unfounded when doses have been carefully adjusted and measured.[184] Although subject to fewer interactions, azathioprine may exacerbate HIV replication, whereas mycophenolic acid antagonizes the antiviral activity of zidovudine and stavudine and enhances the antiviral activity of abacavir.[162] Currently, no clear consensus is available regarding the optimal immunosuppressive regimen for HIV-positive kidney allograft recipients. Interleukin (IL) 2 receptor blockade (basiliximab or daclizumab) as induction therapy has been widely used to avoid initial T-cell depletion. Nonetheless, antithymocyte globulin and alemtuzumab have also been successfully used for induction.[184,185,190,192] Oral immunosuppression has most commonly consisted of a calcineurin inhibitor combined with mycophenolate mofetil or sirolimus with or without long-term low-dose corticosteroid use.[184,185,190,192] For all immunosuppression regimens, HIV-positive recipients of organ allografts require frequent monitoring of drug levels, a high level of suspicion for rejection, and careful attention to infection prophylaxis.

On the basis of existing literature, it is reasonable for HIV-positive patients with ESRD to be offered living donor or deceased donor renal transplant if they have had an undetectable HIV viral load and a stable CD4 cell count of more than 200/μL for 6 months and are free of active OIs. Specific institutional inclusion and exclusion criteria may vary, but national guidelines exist in several countries.[131] Primary care nephrologists should consider referral to a transplant center with established success in transplant for HIV-positive patients. A trial period of combined immunosuppressive and antiretroviral medications before transplant may be useful to ensure subsequent optimal monitoring and dosage.

PATHOGENIC EFFECTS OF HIV INFECTION ON THE KIDNEY

Viral Infection of Renal Cells

A central issue in pathogenesis has been to determine whether HIV can directly infect renal cells. Viral replication is likely restricted by lack of CD4 and chemokine coreceptors required for entry, and transfection of viral constructs allows renal epithelial cells to produce viral particles.[193,194] Furthermore, epithelial cells transfected with CD4 and CXCR4 chemokine receptors support viral replication.[195]

How HIV-1 enters renal cells remains unclear. Lymphocytes may allow epithelial cell infection in a tight monolayer via transcytosis.[196] HIV-1 infection has been demonstrated in vitro for renal epithelial cells derived from children with HIVAN.[197] Interestingly, virus isolated from primary renal epithelial cells derived from HIV-positive individuals appears to be dual tropic, and a genetic variability of gp120 influences renal infectivity.[198] Another possible mechanism of HIV infection of renal cells that traditionally lack coreceptors required for virus entry is via transfer of CCR5 by microparticles released from peripheral blood mononuclear cells.[199] An in vitro model has shown that these small membrane vesicles, which contain cell surface and cytoplasmic components of the original cell, can efficiently transfer CCR5 between cells, thus allowing HIV entry into cell types without endogenous expression of this coreceptor.[199]

Evidence of infection of mesangial cells in vitro is conflicting, although CD4-independent infection requiring an orphan G protein–coupled receptor has been reported.[200] Clear evidence for podocyte infection in vitro is lacking,[8] although in situ hybridization and polymerase chain reac-

TABLE 3. **Summary of HIV Genes and Potential Role in HIV-Related Renal Disease***

HIV gene	Role in HIV life cycle[205]	Evidence for involvement in HIV-related renal disease
gag	Encodes structural proteins of viral core	Transgenic mice expressing HIV genes, but not the *gag* and *pol* genes, still develop FGS, suggesting that *gag* and *pol* are not essential to development of FGS[78]
pol	Encodes essential enzymes in replication and integration	Transgenic mice lacking *gag* and *pol* still develop FGS[78]
env	Encodes viral envelope glycoproteins gp120 and gp41 (derived from precursor gp160); gp120-CD4 interactions essential to cell infectivity	gp160 may modulate proliferation and apoptosis in mesangial cells[206]
vpr	Involved in formation of preintegration complex and nuclear import	FGS and proteinuria develop only in transgenic mice with an intact *vpr* gene; vpr can be localized by immunohistochemical processing to glomerular and tubular epithelia; in combination with tat, can cause FGS in the absence of any other HIV proteins[75]; expression alongside other HIV genes in podocytes alone can result in FGS[79]
nef	Interferes with multiple host cell functions, enhancing viral infectivity at a number of stages of life cycle	May play a role in HIVAN but not essential for the development of glomerular collapse; may also contribute to the severity of tubulointerstitial injury[73,207]; may have a role in podocyte proliferation and dedifferentiation when *nef* is expressed exclusively in podocytes,[208] although not all studies have corroborated these findings[209]; expression alongside other HIV genes in podocytes alone can result in FGS[79]
tat	Transcriptional activator allowing transcription elongation; accelerates viral protein production of proviral genome, up-regulates *rev* and *nef*	Transgenic mice bearing only *tat* and *vpr* genes develop FGS[75]; expression alongside other HIV genes in podocytes alone can result in FGS[79]
rev	Regulates viral RNA expression and splicing; controls viral RNA nuclear export	Expression alongside other HIV genes in podocytes alone can result in FGS[79]
vpu	Promotes intracellular degradation of CD4, enhances release of virus from cell membrane	No current evidence for involvement in HIV-related renal disease
vif	Increases particle infectivity; may increase efficiency of cell to cell transmission of HIV	Expression alongside other HIV genes in podocytes alone can result in FGS[79]

*FGS = focal segmental glomerulosclerosis; HIV = human immunodeficiency virus; HIVAN = HIV-associated neuropathy.

tion have suggested that both renal epithelial cells and podocytes may contain viral RNA and proviral DNA.[69,201] Direct infection of epithelial cells in individuals with HIVAN has also been demonstrated by these techniques.[202]

The potential role of renal dendritic cells in HIV infection has largely been overlooked. Dendritic cells are known to be involved in binding, dissemination, and transfer of HIV to a variety of lymphoid and nonlymphoid tissue and thus may also play an important part in HIV infection of renal cells.[203] C-type lectin receptors such as dendritic cell-SIGN are known to act as HIV capture and attachment factors on dendritic cells, but they may also have an additional role in HIV entry into renal tubular cells. The C-type lectin receptor DEC-205 has been shown in an in vitro model to mediate internalization of HIV into human kidney tubular cells that lack CD4, CCR5, and CXCR4.[204] Thus, increasing evidence suggests that renal cells may support viral replication.

Role of Viral Proteins

A key model for the analysis of renal pathogenesis has been the use of transgenic mice that express particular combinations of viral proteins, but lack *gag* and *pol*, and are therefore incapable of generating complete virions.[8,76] HIV proteins and their potential role in HIV-related kidney disease are summarized in Table 3. Tg 26 mice lack *gag* and *pol* HIV-1 proviral DNA but develop glomerular sclerosis.[78] The renal pathological process appears to require renal expression of the transgene since wild-type mice who underwent a transplant with transgene-expressing kidneys developed nephropathy, whereas transgenic mice who underwent a transplant with wild-type kidneys did not.[77] HIV gene products appear to directly induce cell-cycle progression, leading to epithelial cell dedifferentiation and collapse. Administration of a cyclin-dependent kinase inhibitor, which targets cell-cycle progression, to transgenic mice reduced or reversed renal disease.[210]

Transgenic mouse studies have suggested a role for *vpr*, with or without *tat* expression, in the development of FGS and that macrophage-specific expression of HIV proteins may also be important.[75] Others have suggested that nef contributes to FGS, but not the glomerular collapse observed in HIVAN, and may contribute to the severity of interstitial nephritis.[73,74] Podocyte-restricted expression of *vif*, *vpr*, *nef*, *tat*, and *rev* induced many features of HIVAN in another transgenic model, although the development of a renal disease phenotype was dependent on the genetic background of the mouse.[79] An alternative model in which

nef is expressed using a CD4 promoter showed that nef interaction with p21-activated kinase 2 in thymocytes, macrophages, and dendritic cells was required but not sufficient for the renal manifestations of an AIDS-like disease.[211] Studies have suggested that nef may induce podocyte proliferation[212] and stimulate podocyte dedifferentiation with associated molecular changes, including gain of Ki67.[208] However, findings from other transgenic mouse studies argue against a prominent role for proliferation or apoptosis in HIV protein–related podocyte damage.[209] Of note, such podocyte dedifferentiation and cell cycle progression with no clinical glomerular renal disease have not been described in any human podocyte lesions. Furthermore, the finding of glomerulosclerosis in podocytes after expression of a foreign protein may simply reflect the byproduct of nonspecific podocyte death due to the manipulation, rather than represent a true causal relationship between specific HIV-1 proteins and podocyte glomerulosclerosis. For example, the development of glomerulosclerosis has been demonstrated after diphtheria-toxin induced selective podocyte death in a rat model, which supports the hypothesis that podocyte depletion per se may be the major mechanism for glomerulosclerosis in a variety of renal diseases.[213]

Another feature of HIV-1 infection is development of apoptosis in renal epithelial cells, which is mediated by Fas up-regulation, and caspase activation in both murine models and HIVAN specimens.[83,214] As in T cells, Fas-mediated apoptosis may be dependent on gp120 for cell sensitization.[215] gp160 may contribute to mesangial cell apoptosis in HIVAN, which is tumor necrosis factor α dependent and associated with down-regulation of the antiapoptotic protein Bcl-2.[206]

Host Factors

The host response to HIV infection may influence the disease phenotype through the activation of specific cytokine pathways. A microarray experiment showed that many mediators of the inflammatory response, including cytokines, chemokines, and adhesion molecules, were up-regulated in renal epithelial cells isolated from a patient with HIV-associated renal disease in response to HIV-1 proteins.[216] Many of the up-regulated genes were targets of IL-6 and NF-κB regulation. The potential role of the NF-κB pathway in HIVAN was also demonstrated in a murine model with HIV expression restricted to $CD4^+$ lymphoid tissue, in which inhibition of this pathway led to a reduction in $CD45^+$ memory T cells infiltrating the kidney and an improvement in renal histopathological changes.[217] HIV-1 gp120 treatment of renal tubular cells in vitro stimulates expression of the monocyte chemoattractant protein 1.[218] Both IL-6 and tumor necrosis factor α expression by human mesangial and tubular epithelial cells in turn stimulate HIV-1 expression in infiltrating monocytes to further drive proinflammatory cytokine production.[219] The proinflammatory microenvironment in the kidney of patients with HIVAN also contains interferon-α and TGF-β.[220] The TGF-β contributes to tubular regeneration and up-regulates the replication of HIV-1 in human mesangial cells.[221] Expression of TGF-β is enhanced in HIV-associated FGS[81,221] and up-regulated after gp120 exposure of renal tubular cells in vitro.[218] However, the role of inflammatory mediators in the pathogenesis of HIVAN and their exact relationship to expression of HIV-1 proteins in renal tissue is not entirely clear. A case report of a patient in whom clinical and histopathological resolution (including interstitial infiltrate) of HIVAN after commencement of HAART demonstrated similar proportions of tubular epithelial cells and glomerular podocytes expressing HIV-1 messenger RNA before and after treatment, suggesting that intracellular expression alone of HIV-1 RNA in renal cells is insufficient in the pathogenesis of HIVAN.[69]

Chronic HIV infection is characterized by high serum immunoglobulin levels. Immune complexes that contain HIV may circulate in the systemic circulation and may be deposited in the renal microcirculation, giving rise to a range of glomerulonephropathies often collectively referred to as *HIV immune complex kidney diseases*.[8]

Alterations in Renal Microvasculature

Endothelial dysfunction and abnormalities of the clotting cascade with deposition of thrombi and platelets in the vessel wall are features of HIV-1 pathogenesis.[106] Understanding how HIV affects renal capillaries and arterial microvessels is central to understanding the mechanism of TMA and potentially other HIV-associated renal diseases. HIV proteins trigger Fas-mediated apoptosis of endothelial cells.[222] Whether these changes require direct viral replication in the kidney is unclear. In a macaque model with HIV-2–induced progressive immunosuppression, macaques that developed TMA lacked evidence of renal viral replication, although the techniques used to detect replication were not ultrasensitive.[223] Mild clinical features of TMA preceded relevant immunosuppression. During HIV-related TMA, fibroblast growth factor (FGF) 2 expression is increased.[224] A model has been proposed, using results from animal models and children with TMA, in which increased synthesis and release of FGF-binding protein by regenerating renal tubular epithelial cells could bind FGF-2 produced in renal glomerular and tubular epithelial cells, thus preventing its binding to heparin sulfate proteoglycans in the renal interstitium and its induction via the FGF-2 receptor of endothelial cell growth and survival.[224-226] Although increased FGF-binding protein is observed in other

conditions, including HIVAN, the level is most marked in TMA.[225] In addition, expression of tumor necrosis factor α and IL-1β is enhanced during HIV infection in the kidney, and these cytokines up-regulate adhesion molecule expression on endothelial cells, further driving renal inflammation[227] and potentially contributing to alterations in regulation of the clotting cascade. The coagulation abnormalities that are a feature of TMA in HIV infection include up-regulation of tissue plasminogen activator. However, in one series, levels of plasminogen activator inhibitor type 1 were not increased compared with a control group of HIV-positive individuals without TMA, even though they are a feature of HIV-negative TMA cases, suggesting fibrinolytic defects may be less important to TMA pathogenesis in HIV-positive cases.[228] Down-regulation of von Willebrand factor cleaving protease (ADAMTS13), a metalloprotease that cleaves multimers of von Willebrand factor on platelets, is a key feature of TMA, and a case report illustrated that antibodies against this protease can be a feature of HIV-associated TMA.[229]

The renal manifestations of HIV disease are commonly the result of viral replication in renal cells and/or recruited immune cells and may be modified by pathologic process in the renal microcirculation. Disease phenotype is further influenced by both viral and host genetic variation. The complex nature of this interaction is illustrated by the observation in mouse models that renal disease is independent of CD4 depletion yet associates with some specific features of HIV infection, such as the ability of nef to induce CD4 down-regulation on T cells and to induce apoptosis.[207]

CONCLUSION

Chronic kidney disease is an important complication of chronic HIV infection, and all patients with newly diagnosed HIV infection should be screened for the presence of CKD. HAART, blood pressure control, and management of dyslipidemia may reduce the risk of cardiovascular complications of CKD and slow the progression to ESRD. For individuals who develop ESRD, renal transplant is increasingly an option.

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