HIV-Associated Renal Diseases and Highly Active Antiretroviral Therapy–Induced Nephropathy

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Renal disease is becoming an increasingly prevalent entity in human immunodeficiency virus (HIV)–infected patients; it occurs in a variety of clinical settings and is associated with histopathological changes. HIV-related renal impairment can present as acute or chronic kidney disease; it can be caused directly or indirectly by HIV and/or by drug-related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vaculopathy and renal damage. Acute renal failure is frequently caused by the toxic effects of antiretroviral therapy or nephrotoxic antimicrobial substances used in the treatment of opportunistic infections. Chronic renal disease can be caused by multiple pathophysiological mechanisms, leading to HIV-associated nephropathy, a form of collapsing focal glomerulosclerosis, thrombotic microangiopathy, and various forms of immune complex glomerulonephritis. The increase in life expectancy and alteration of lipid metabolism due to receipt of highly active antiretroviral therapy are expected to result in an increased prevalence of diabetes and hypertension and, thus, to secondary diabetic and hypertensive renal damage. Antiretroviral agents, such as indinavir and tenofovir, have been associated with nephrotoxic drug effects that have been shown to be reversible in most cases. In this article, we review the current knowledge about acute and chronic HIV-associated renal disease, metabolic alterations and related nephropathies, and toxic drug effects of combination antiretroviral pharmacotherapy.

Nephropathy is a common finding in patients infected with HIV, and it necessitates increased surveillance and adaptation of dosages of HIV drugs. Direct effects of HIV seem to play a major role in the development of HIV-associated nephropathy (HIVAN) and thrombotic microangiopathy. Improved survival among patients with HIV infection is anticipated to result in an increase in the long-term development of HAART-associated metabolic complications, such as diabetes and dyslipidemia, which, in turn, can contribute to vascular changes and decreased renal function. Since the introduction of HAART, a variety of renal side effects and adverse drug reactions have been recognized and vary from the development of proteinuria to acute renal failure.

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ACUTE RENAL FAILURE IN HIV-INFECTED PATIENTS

Acute renal failure in HIV-infected persons can be caused by the same mechanisms that cause it in HIV-uninfected patients. Data from the HAART era are rare, although a recent study that evaluated the incidence and etiology in a prospective analysis of 754 HIV-infected patients reported an incidence of 5.9 cases of acute renal failure per 100 patient-years [1]. Drugs used for treatment of HIV infection that are associated with nephrotoxicity include aminoglycosides, amphotericin, foscarnet, trimethoprim-sulfamethoxazole, tenofovir, indinavir, and acyclovir [2]. Furthermore, acute renal failure may be related to thrombotic thrombocytopenic purpura–hemolytic uremic syndrome or pharmacotherapy, which will be discussed below with the respective substances. Acute renal failure is a common

finding in HIV-infected patients and is associated with advanced stages of HIV infection (i.e., CD4 cell count of <200 cells/mm^3 and HIV RNA level of >10,000 copies/mL), hepatitis C virus coinfection, and a history of antiretroviral treatment [1].

CHRONIC RENAL DISEASE IN HIV-INFECTED PATIENTS

The prevalence of chronic kidney disease in the various stages of HIV infection is difficult to assess. Proteinuria and elevated creatinine level have been found in 7.2% [3] to 32% [4] of HIV-seropositive patients and were associated with an increased rate of death in a study of 2038 female HIV-infected patients [5]. Proteinuria still remains a nonspecific finding in HIV-infected patients. Autopsy studies yield a prevalence of up to 43% of pathological changes on histological examination [6]. Both autopsy and biopsy studies may be limited by bias of selecting subjects presenting with apparent renal disease. HAART has been found to reduce progression from AIDS to end-stage renal disease in patients of African descent by 38%, yet a significant increase in the prevalence of end-stage renal disease (ESRD) associated with an increase in the prevalence of HIV infection in this population has been predicted [7]. Even though exact epidemiologic data are missing because of the use of different screening techniques, chronic kidney disease in HIV-infected patients is a common and clinically relevant finding. The cause of chronic renal disease in HIV-infected patients can be difficult to assess on clinical grounds alone and can most often only be determined by renal biopsy.

NEPHROPATHY ASSOCIATED WITH HIV INFECTION

Several types of renal disease seem to be directly or indirectly caused by HIV: classic HIVAN, HIV-associated thrombotic microangiopathy, and HIV-associated, immune-mediated glomerulonephritides [2].

HIVAN. Classic HIVAN is a syndrome caused by focal sclerosing glomerulopathy with severe proteinuria, renal failure, and rapid progression to ESRD. It has become the most common cause of ESRD in HIV-1–seropositive patients. HIVAN primarily occurs in patients of African descent [8–11], suggesting a genetic predisposition to the disease. Duffy antigen/receptor for chemokines has controversially been discussed as a candidate gene involved in the development of HIVAN [12, 13]. The estimated prevalence of HIVAN has ranged from 3.5% in clinical studies to 12% in autopsy studies [14]. Because HIVAN typically occurs late in the course of HIV-1 infection [15], risk factors for the development of HIVAN include a CD4 cell count <200 cells/mm^3 and a high viral burden.

Clinical features of this syndrome include advanced renal failure and proteinuria (the protein level is often—but not necessarily—at a nephrotic level [>3 g/day]) [16, 17], a lack of peripheral edema despite the severe loss of protein, and, frequently, enlarged kidneys visible on renal ultrasound [9].

Renal biopsy is the only means to establish the diagnosis of HIVAN. Characteristic histological findings include collapsing focal and segmental glomerulosclerosis, tubular epithelial atrophy with microcystic dilatation of the tubules [18], and lymphocytic interstitial infiltration. Viral infection of renal cells seems to play an important role in the pathogenesis of HIVAN. In 1989, Cohen et al. [19] reported detection of HIV-1 in renal epithelial cells by DNA in situ hybridization. Transgenic mouse models have been described in which expression of a *gag/pol*-deleted provirus leads to HIVAN-like histological changes [20] or in which the single HIV-1 gene *nef* can lead to immunodeficiency and renal disease [21]. HIV can be detected in biopsy specimens from the renal epithelium in humans and can replicate in renal epithelial cells, even in patients who are receiving effective antiretroviral therapy [22]. In 2002, a study was published demonstrating a tissue-specific evolution of HIV-1 gp120 DNA sequences in renal epithelial tissues that was different from those observed in PBMCs, suggesting that renal epithelial cells are capable of complete viral replication and represent a separate compartment for HIV-1 [23].

Without adequate treatment, the prognosis of HIVAN is poor. Usually, HIV-associated nephropathy is diagnosed at a late stage, and untreated patients frequently have progression to ESRD within a few months [10]. The most effective therapeutic option seems to be HAART. Cases have been documented in which initiation of antiretroviral treatment led to clinical and histological remission within a few weeks [24]; other patients ended dialysis treatment [25]. HAART also seems to have a protective renal effect. In a 12-year follow-up study of 3976 HIV-1–seropositive patients, a 60% reduction in the risk of development of HIVAN associated with HAART was found [26]. Although there is strong observational data supporting a role for HAART in the treatment of HIVAN, no prospective, randomized, controlled trials have been performed that support a beneficial effect of HAART or of other medical therapies. Several studies with limitations resulting from lack of randomization or small size seem to support a beneficial effect of angiotensin-converting enzyme inhibitors [27]. Because trials involving prednisone have been rare in the HAART era, there is not enough evidence to generally support treatment of HIVAN with corticosteroids [28].

Thrombotic microangiopathy. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura present a spectrum of diseases characterized by hemolytic anemia, thrombocytopenia, and renal insufficiency and clinical features, such as fever and neurological manifestations. Several reports have linked thrombotic microangiopathy

to HIV infection, suggesting that HIV proteins may mediate endothelial dysfunction, leading to platelet deposition in the microvasculature [29]. Several potential underlying mechanisms have been discussed: HIV-1 p24 antigen has been detected in endothelial cells in patients with thrombotic thrombocytopenic purpura [30]; secretion of inflammatory cytokines, such as TNF-α and IL-1β [31], leading to endothelial cell retraction has been documented; and renal endothelial cell apoptosis and inhibition of von Willebrand factor–cleaving protease have been linked to HIV-induced thrombotic microangiopathy [32].

Typical clinical features of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome are onset at ~35 years of age, a predominance among male subjects, and poorer outcome, compared with idiopathic forms of the disease [33]. Therapeutic options consist of plasma infusion and plasmapheresis, which have had variable success. Other attempted therapies include glucocorticoids, immunoglobulin infusions, antiplatelet drugs, vincristin, and splenectomy, although general treatment recommendations are lacking.

Immune complex–mediated glomerulonephritis. A multitude of immune complex–mediated glomerulonephritides have been reported as causes of chronic kidney disease in HIV-infected patients. The prevalence of HIV-associated, immune complex–mediated glomerulonephritides has been estimated to be 15%–80%. A study of 60 biopsy specimens found that some form of immune complex–mediated glomerulonephritis was present in 37% of biopsy specimens, sometimes concordant with HIVAN-like changes. The authors classified their findings into 4 categories: immune complex–mediated glomerulonephritis, IgA nephritis, mixed sclerotic/inflammatory disease, and lupus-like syndrome [34]. Immune complex–mediated glomerulonephritis may present as postinfectious glomerulonephritis, membranous nephritis, IgA nephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis [2].

IgA nephritis seems to be more prevalent among European patients, with mesangial IgA deposits being detected in 7.75% of all HIV-infected patients in a postmortem study [35]. A recent report estimated that the prevalence of lupus-like nephritis, characterized by immunoglobulin (IgG, IgA, and IgM) and complement (C3 and C1q) deposits, in the absence of serologic markers for systemic lupus erythematodes, was 17% [36].

In general, HIVAN is mainly limited to patients of African descent, whereas most cases of renal disease in the white population seem to be immune complex–mediated glomerulonephritis [37]. Despite the lack of randomized trials, patients with HIV-associated, immune complex–mediated glomerulonephritis seem to benefit from treatment with angiotensin-converting enzyme inhibitors, glucocorticoids, and antiretrovirals [38, 39].

METABOLIC ALTERATIONS ASSOCIATED WITH ANTIRETROVIRAL TREATMENT

Metabolic alterations associated with HAART may lead to significant elevations in serum lipid levels, accelerating the development of diabetes and the metabolic syndrome. Long-term metabolic changes will possibly cause an increase in diabetic and hypertensive renal disease as well as vascular complications.

Diabetes mellitus. Antiretroviral therapy has been associated with impaired glucose tolerance [40, 41]. A study of 17,852 HIV-seropositive patients evaluated the prevalence of cardiovascular risk factors and reported a prevalence of diabetes of 2.5% that was significantly associated with antiretroviral treatment [42]. A controlled study evaluated 1689 patients and reported an incidence of diabetes of 14% among patients who were receiving antiretroviral therapy and demonstrated a 4-fold risk of developing diabetes in the HIV-infected group [43]. The apparent increase in the incidence of diabetes may be the result of methodological differences or may be an expression of the elevated risk of developing diabetes associated with HAART-induced metabolic changes and an increased survival duration. Data on the prevalence of secondary damage due to diabetes, such as nephropathy, retinopathy, or polyneuropathy, are lacking.

Hypertension. The findings of studies assessing HAART-associated hypertension are inconsistent [42]. A recent study that observed a cohort of 5578 patients during 1984–2003 revealed an incidence of hypertension in 7.3% among HIV-seropositive patients who had a systolic blood pressure >140 mm Hg, and the incidence began to increase significantly after 2 years of antiretroviral therapy. The risk of developing hypertension was maximally elevated (OR, 1.7) after >5 years of treatment with HAART, compared with the risk among HIV-infected patients who did not receive treatment (OR, 0.79) [44].

A study that evaluated 98 renal biopsy specimens obtained from HIV-1–seropositive patients with clinical evidence of nephropathy revealed diabetic glomerulopathy in 6 patients (6.1%) and hypertensive nephrosclerosis in 4 patients (4.1%) [45]. Additional biopsy studies can only be performed ethically in the stage of severe renal impairment, thus possibly leading to false conclusions resulting from selection bias. Because moderate forms of diabetic and hypertensive glomerulopathy cannot be confirmed by examination of biopsy specimens, the true incidence of metabolic renal disease remains unknown.

RENAL ADVERSE EFFECTS OF HAART

Renal damage caused by antiretroviral drugs can result in a variety of toxic drug effects presenting as acute renal failure, tubular necrosis, kidney stones, or chronic renal disease.

Protease Inhibitors

Indinavir. Indinavir is the protease inhibitor that has been most frequently associated with adverse renal effects, including nephrolithiasis, crystalluria, dysuria, papillary necrosis, and acute renal failure [46]. In 1997, a study demonstrated that urinary crystals composed of indinavir occurred in 20% of all patients who used indinavir, and the condition progressed to nephrolithiasis in 3%. Other patients without detectable stone formation (12.5%) presented with symptoms of dysuria and flank pain [47]. A study of 1219 patients estimated that the incidence of urological complications was 8.3 cases per 100 treatment-years [48]. Stone formation can occur in any structure of the kidney and the urinary tract, with risk factors being a urine pH >6, low lean body mass level, high concentrations of indinavir, environmental influences (such as a warm climate) [48], concomitant treatment with trimethoprim-sulfamethoxazole [49] or acyclovir [50], and concordant chronic hepatitis B or C virus infection [51]. Antiretroviral therapy given in combination with low-dose ritonavir seems to increase the renal toxicity of indinavir [52]. The safest way to avoid urological symptoms seems to be maintenance of a high urinary output of 1500 mL/day. After acute renal failure occurs, it appears to be safe to restart indinavir treatment once adequate rehydration is established. Acidification of the urine is expected to be poorly tolerated and possibly harmful [53]; thus, no recommendation to lower the urinary pH has been issued to date.

An increase in the serum creatinine level frequently preceded by sterile leukocyturia has been observed with indinavir treatment in 14%–33% of patients [54–58]. Most urologic symptoms and elevations in serum creatinine levels normalize within weeks after the discontinuation of indinavir, although irreversible renal toxicity has been reported. Interstitial nephritis was demonstrated in renal biopsy specimens; this can have a self-limited course [59, 60] or lead to interstitial fibrosis [61] and renal atrophy [62].

Ritonavir. Case reports have linked ritonavir use to reversible renal failure [63, 64]. All reported patients who showed an increase in the serum creatinine level received ritonavir at a therapeutic dose of 800–1200 mg per day. In 1 patient who had acute renal failure after exposure to ritonavir, rechallenge with a lower dose of ritonavir (200 mg) led to a second (yet reversible) decline in renal function [65]. The majority of reported patients had received concomitant medication with potentially nephrotoxic drugs or had other underlying renal pathology, such that specific cases of nephrotoxicity attributable to ritonavir use have not been definitely established.

Saquinavir and nelfinavir. Saquinavir and nelfinavir have been demonstrated to have a generally safe renal safety profile in controlled trials, but for both drugs, there have been single case reports suggesting the potential for inducing renal calculi [66]. Analysis of a urinary stone revealed a composition of 99% nelfinavir and 1% indinavir—a drug that had been discontinued before treatment with nelfinavir had been started [67].

Atazanavir. Atazanavir has not been associated with renal toxicity in clinical trials. However, a recent case report described a patient with interstitial nephritis and reversible acute renal failure after addition of atazanavir to an otherwise stable HAART regimen. The therapeutic regimen included potentially nephrotoxic drugs, and examination of a renal biopsy specimen revealed histological changes of HIVAN, with collapsing glomerulosclerosis and interstitial nephritis [68].

Other protease inhibitors. Protease inhibitors, such as amprenavir, fosamprenavir, and lopinavir, have not been associated with severe renal disease to date.

Nucleotide Reverse-Transcriptase Inhibitors

Tenofovir, adefovir, and cidofovir are acyclic nucleoside phosphonates that have been associated with renal tubular damage. The renal adverse effects may cause a variety of clinical presentations varying from tubule cell death, such as acute tubular necrosis, to possibly reversible tubular dysfunction, such as Fanconi syndrome.

A number of case reports linked tenofovir to tubular toxicity and Fanconi syndrome with variable severity [69–80]. Fanconi syndrome consists of a generalized defect of membrane transporters in the proximal tubule, leading to renal loss of glucose (despite a normal serum glucose concentration), as well as a loss of phosphate, calcium, uric acid, amino acids, bicarbonates, and tubular proteins [81]. Most cases associated with tenofovir use do not meet the criteria for Fanconi syndrome but present as severe tubular dysfunction with an elevation in creatinine levels, hypophosphatemia, and glycosuria [79]. Renal biopsy reveals tubular damage or acute tubular necrosis without involvement of the glomeruli [69–72]. Risk factors include low body weight, impaired renal function at baseline, and concomitant receipt of nephrotoxic drugs [77, 78]. In general, tubular dysfunction is reversible after withdrawal of tenofovir [78, 79], although persistent renal damage with impairment of renal function has been reported [17, 72]. Approximately 55 cases of tubular dysfunction in association with tenofovir use have been reported in the literature. The incidence of renal tubular dysfunction is difficult to assess, because these cases are anecdotal, and the incidence has not been reported in larger, well-controlled studies.

Recent reports have linked HAART regimens that contain tenofovir to a mild, time-dependant elevation in the serum creatinine level [82–84] and a decrease in the glomerular filtration rate. One study of 174 patients found a lower mean glomerular filtration rate, as calculated by creatinine clearance (97 mL/min [1.73 m^2] vs. 107 mL/min [1.73 m^2]), with 38%

of patients showing an impaired glomerular filtration rate in the tenofovir arm compared to 29% in the control group [85]. The decrease in glomerular filtration rate in those on a tenofovir-containing regimen remained well within the normal range of glomerular filtration rate and did not lead to discontinuation of tenofovir.

Nephrotoxicity may be caused by an imbalance of influx and efflux of drugs into renal cells, thus leading to an increase in the intracellular drug concentration [86]. Influx of tenofovir into renal tubular cells is mediated via the human organic anion transporter 1 [87]. Efflux pumps responsible for the apical efflux of tenofovir out of proximal tubule cells have not been identified, but on the basis of its transportation of adefovir [88], it has been hypothesized that the multidrug-resistance protein 4 is responsible for transporting tenofovir into the tubular lumen [89]. Because ritonavir has been associated with inhibition of multidrug-resistance protein 2, an efflux pump for organic anions, it has been hypothesized that the interactions between ritonavir and multidrug-resistance proteins may result in a decreased efflux of tenofovir, leading to a toxic increase in intracellular drug concentration [89]. This hypothesis is supported by clinical reports describing tenofovir-associated tubular renal dysfunction mainly in patients receiving salvage therapy who are receiving concurrent ritonavir treatment [89]. Inhibition of multidrug-resistance protein 4 by ritonavir has not yet been described [90, 91].

In a 3-year study that compared 602 therapy-naive patients with a backbone of lamivudine and efavirenz treatment with either tenofovir or stavudine, no difference in the incidence of renal dysfunction was found [92]. A recent evaluation of the same study population demonstrated that only 2 patients in the tenofovir arm developed grade 2 nephrotoxicity (defined as increase in the serum creatinine level of 2.1–3.0 mg/dL) that resolved with continued treatment. Overall results were similar to those for the control group, and severe nephrotoxicity did not occur [79]. In all randomized, double-blinded studies, tenofovir has been demonstrated to have a renal safety profile similar to that of other combination therapies [93–95] and to have an overall low potential for nephrotoxicity. Renal tubular dysfunction seems to be an uncommon but important adverse effect of therapy with tenofovir.

Nucleoside Reverse-Transcriptase Inhibitors

Renal toxicity associated with the use of nucleoside analogues is generally rare. Case reports have demonstrated that didanosine [96, 97] and lamivudine-stavudine treatment have been associated with tubular dysfunction or Fanconi-like syndrome [98]. Another report described acute renal failure and biopsy-proven interstitial nephritis after exposure to abacavir [99].

Nonnucleoside Reverse-Transcriptase Inhibitors

Data regarding renal toxicity with nonnucleoside reverse-transcriptase inhibitors use are limited, because nevirapine, efavirenz, and delavirdine have been demonstrated to have a safe renal profile in controlled trials. A single case report linked efavirenz to renal toxicity on the basis of a hypersensitivity reaction involving pneumonitis, hepatitis, and interstitial nephritis; symptoms recurred after a rechallenge. [100].

Fusion Inhibitors

Enfuvirtide has not been associated with severe renal adverse effects. In a safety analysis of 663 patients in the T-20 versus Optimized Regimen Only (TORO)–1 and TORO-2 trials, 1 case patient who had a history of diabetes, proteinuria, and hematuria developed membranoproliferative glomerulonephritis [101].

SUMMARY

Renal pathology in HIV-infected persons can be caused by a variety of mechanisms leading to a broad spectrum of clinical disease. HIV itself seems to directly mediate the development of HIVAN and thrombocytopenic purpura. Other pathophysiological pathways comprise indirect viral effects, such as renal immune complex deposition. Long-term survival contributes to an increase in HAART-induced metabolic alterations, diabetes, and hypertension and is likely to be associated with an increase in secondary renal damage, such as hypertensive nephrosclerosis and diabetic glomerulopathy. For the majority of antiretroviral substances, HAART-related effects on renal function do not seem to be highly relevant with regard to nephrotoxicity. Still, indinavir has been associated with frequent renal and urological adverse effects and with stone formation. Despite a safe renal profile in clinical trials, a number of case studies have reported tubular dysfunction associated with tenofovir use. In large, controlled clinical trials, the incidence of renal abnormalities in the treatment arm did not differ from that in the control arm.

The expected increase in the incidence of renal disease and end-stage renal failure might, to some extent, be prevented by close monitoring of renal function, including an estimation of creatinine clearance before HAART is initiated, and continued monitoring during treatment—specifically, for patients receiving late-stage HIV therapy and in the context of a large number of coadministered medications. Any changes in serum creatinine level or the development of proteinuria should lead to an early investigation of the cause. Prompt recognition should induce studies that evaluate the different therapeutic options in larger clinical trials. Until then, clinicians should be aware of the increasing numbers of HIV-seropositive patients with renal pathology who frequently require special attention, as well as the need to alter doses for patients with renal impairment.

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