EXPERT REVIEWS

Predictors of HIV-associated nephropathy

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Renal disease accounts for significant morbidity and mortality in patients with HIV-1 infection. HIV-associated nephropathy (HIVAN) is an important cause of end stage renal disease in this population. Although multiple genetic, clinical, and laboratory characteristics such as Apolipoproetin-1 genetic polymorphism, high viral load, low CD-4 count, nephrotic range proteinuria, and increased renal echogenicity on ultrasound are predictive of HIVAN, kidney biopsy remains the gold standard to make the definitive diagnosis. Current treatment options for HIVAN include initiation of combined active antiretroviral therapy, blockade of the renin-angiotensin system, and steroids. In patients with progression of HIVAN, renal transplant should be pursued as long as their systemic HIV infection is controlled.

Keywords: APOL1 • dialysis • HIV • HIVAN • kidney transplant

Renal disease is one of the major causes of mortality in HIV-1-infected patients along with malignancy, cardiovascular and liver disease [1]. The risk of death in HIV-1-infected patients is increased by almost sixfold in those with acute kidney injury (AKI) and chronic kidney disease (CKD) [2,3]. HIV-1-infected patients are at risk for proteinuria, AKI, immune complex disease, thrombotic microangiopathy (TMA), medication-induced nephrotoxicity and HIV-associated nephropathy (HIVAN) [4]. A summary of different forms of renal involvement in HIV-1-infected patients is listed in Box 1. This review highlights the different renal disorders in HIV-1-infected patients, emphasizing the pathogenesis and clinical predictors of its most aggressive form, HIVAN.

Proteinuria

Up to 30% of patients infected with HIV are at risk of developing proteinuria. The presence of microalbuminuria is a predictor for development of overt proteinuria [5]. Furthermore, an albumin to creatinine ratio of greater than 10 mg/g, with no evidence of kidney disease at baseline has been demonstrated to be an independent risk factor for development of renal dysfunction [6]. The presence of albuminuria and overt proteinuria is associated with increased cardiovascular morbidity and mortality in this population [7,8]. Therefore, strategies to prevent or slow down the progression of proteinuria, such as improved blood pressure control, the blockage of renin–angiotensin–aldosterone system and treatment of dyslipidemia should be implemented whenever appropriate.

Acute kidney injury

AKI is frequent in HIV-1-infected patients with incidence rates as high as 5.9/100 person-years [9]. In a retrospective study of HIV-infected hospitalized patients, which included 52,580 HIV-infected patients in 1995 and 25,114 in 2003, HIV-infected patients had an increased incidence of AKI in both the pre-combined active antiretroviral therapy (cART) (adjusted odds ratio [OR]: 4.62; 95% CI: 4.30–4.95) and post-cART eras (adjusted OR: 2.82; 95% CI: 2.66–2.99). Higher incidence of AKI was associated with increased age, diabetes mellitus, CKD, acute or chronic liver failure and hepatitis coinfection [2]. Other risk factors include male sex, CD4 cell count <200 cells/mm^3 and HIV-1 RNA levels >10,000 copies/ml [9]. Common causes for AKI in HIV-1-infected patients are similar to noninfected individuals. Prerenal states (volume depletion, heart failure and cirrhosis) account for 39% of cases, and acute tubular necrosis accounts for another 37% [9].

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Box 1. Causes of kidney disease in HIV-infected patients.

HIV-related kidney diseases

- HIV-associated nephropathy
- HIV-associated immune complex kidney disease
- Drug-induced kidney disease (Tenofovir-induced proximal tubular dysfunction, protease inhibitor-induced crystalluria)
- Thrombotic microangiopathy

Non-HIV-related kidney diseases

- Membranoproliferative Glomerulonephritis
- Membranous nephropathy
- Postinfectious Glomerulonephritis
- Immunoglobulin A glomerulonephritis
- Amyloidosis
- Acute interstitial nephritis
- Acute tubular necrosis
- Diabetic nephropathy
- Hypertensive kidney disease

HIV-1-associated immune complex kidney disease

Various immune complex kidney diseases have been reported in patients with HIV-1 infection, such as postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, membranous nephropathy, immunoglobulin A nephropathy and diffuse proliferative lupus-like glomerulonephritis [10,11]. This group of renal pathology is characterized by deposition of complement with or without immunoglobulins. In general, patients with HIV-1-associated immune complex kidney disease (HIVICK) have better renal prognosis compared to patients with HIVAN. In a nested case–control study of 751 HIV-1-infected patients, the incidence of end-stage renal disease (ESRD) in patients with HIVICK was 32% at 2 years, which is lower than in patients with HIVAN [12].

Thrombotic microangiopathy

TMA in patients with HIV-1 infection does not differ clinically from the noninfected patients with this disorder. Advanced immunosuppression, opportunistic infections and various drugs commonly used in advanced disease are all considered to be potential risk factors [13–15]. Systemic TMA is a rare complication of HIV-1 infection and based on a large observational cohort of 6022 patients, the incidence of isolated renal TMA is only 0.3% [16]. The measurement of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) level is critical in these patients as treatment with plasma exchange is helpful in repleting this enzyme in patients with low enzyme activity [17].

Medication-induced nephrotoxicity

Some antiretroviral drugs have potential nephrotoxic effects and can contribute to the development of CKD [18–20].

Tenofovir, a nucleoside reverse transcriptase inhibitor, can lead to renal dysfunction [21]. It causes proximal tubular dysfunction, Fanconi syndrome and nephrogenic diabetes insipidus [22–24]. The exact mechanism of nephrotoxicity is unknown, but it is hypothesized that apoptosis of tubular cells and inhibition of mitochondrial DNA replication is involved [25,26]. Polymorphism in the genes encoding for renal transporters involved in tenofovir renal elimination has also been suggested to increase the risk of nephrotoxicity [27]. A study that included 10,841 HIV-infected patients from the Veterans Health Administration over a 10-year period showed that each year of tenofovir exposure was associated with a 33% (18–51%; $p < 0.0001$) increased risk of CKD [28]. Based on these findings, biannual monitoring of serum creatinine, serum phosphate, nondiabetic or controlled diabetic glycosuria and proteinuria for patients on tenofovir with glomerular filtration rate (GFR) <90 ml/min is recommended by Infectious Disease Society of America [29].

Indinavir, ritonavir and atazanavir are protease inhibitors that have been associated with nephrolithiasis, crystalluria, papillary necrosis, acute interstitial nephritis and CKD [30–32].

Elvitegravir is an integrase inhibitor which is coadministrated with cobicistat, a CYPP450 inhibitor, allowing once-a-day dosing of the drug [33]. Although cobicistat has no inherent nephrotoxicity, it inhibits tubular secretion of creatinine through the multidrug and toxin extrusion protein efflux 1 at the apical membrane of the proximal tubular cells. This leads to an increase in plasma creatinine concentration without affecting the actual GFR. Similarly, dolutegravir (an integrase inhibitor) inhibits the tubular secretion of creatinine through the organic cation transporter at the basolateral membrane of the proximal tubular cells, raising plasma creatinine concentration without affecting the actual GFR [34].

HIV-1-associated nephropathy

HIVAN is the prototype of kidney disease associated with HIV-1 infection and was first described in 1984 [35].

Epidemiology

HIVAN predominantly affects HIV-1-infected patients of African ancestry, and its prevalence has been estimated to be as high as 3.5% in the HIV-1-infected population [36]. A decade ago, HIVAN was the leading cause of ESRD in HIV-1-infected individuals, but with the widespread use of cART and early detection of HIV-1 infection, the incidence of HIVAN has decreased [37–39]. In a study of 88 HIV-1-infected patients, it was shown that with an increase in the use of cART over time, the percentage of HIVAN decreased from 75 to 29% in the group with focal segmental glomerulosclerosis morphology on a renal biopsy [40]. Other causes of CKD like hypertension, diabetes, drug-related toxicities, classic focal segmental glomerulosclerosis and HIVICK have become more common over the recent years [12,39,40]. A possible explanation of this is that the use of cART can lead to altered lipid metabolism, dysregulation of glucose

control and lipodystrophy, which are traditional risk factors contributing to the development of CKD [40].

Clinical presentation

Classically, HIVAN presents with rapidly declining GFR and nephrotic range proteinuria [41,42]. Lower extremity swelling and hypertension are uncommon in patients with HIVAN, which may lead to a delay in diagnosis [43]. Other glomerular disorders can have a clinical presentation similar to those with HIVAN and should be considered in this population (Box 2).

Prognosis

The natural history of HIVAN before the advent of cART therapy was quite aggressive with progression to ESRD occurring within 2–4 months. With the advent of cART, prognosis has substantially improved although these patients continue to do worse compared to patients with an alternate cause of kidney disease. In a study of 152 HIV-1-infected patients, 35% had biopsy-proven HIVAN, and those patients were more likely to require dialysis ($p < 0.0001$) in addition to having worse overall survival ($p = 0.02$) [42].

Pathogenesis

Our knowledge regarding the pathogenesis of HIVAN has been evolving. In animal models, HIV-1 gene expression in kidney cells is required for the development of disease [44]. In humans, proviral DNA was found in the renal tissue of all patients with HIVAN even if they had undetectable plasma HIV-1 RNA levels [45]. This suggests that the kidney acts as a compartment separate from blood, and HIV-1 can replicate in the kidney even in patients who achieve serological viral suppression with treatment [46]. The nonstructural gene products of HIV-1, negative effector and viral protein r are involved in the pathogenesis [47,48]. Zuo *et al.* showed that podocyte-restricted expression of negative effector or viral protein r in murine models resulted in the clinical and pathological features of HIVAN [48]. Cytopathic effects of HIV gene products, apoptosis induced by HIV infection and elaboration of cytokines, are all thought to be responsible for the development of HIVAN [49].

Recent studies have shown that HIV-1 infection downregulates expression of miRNAs in human podocytes which contributes to the proliferative phenotype of HIVAN [50]. HIV-1-infected podocytes have an increased expression of markers of proliferation, Ki-67 and cyclins and decreased expression of cyclin-dependent kinase inhibitors, suggesting that these highly differentiated cells re-enter the cell cycle [51]. Furthermore, they have persistent activation of NF-κ B and increased VEGF expression increasing podocyte proliferation [52,53]. However, these proliferative cells may be of parietal rather than visceral origin, which has been demonstrated by some investigators [54].

Genetic predisposition

In studies of adults with HIVAN, 87–97% of the patients are of African descent [55,56]. Initially, nonmuscle myosin heavy chain 9 was thought to be the major genetic risk factor for developing HIVAN in African Americans. However, this increased risk has been demonstrated to be driven by polymorphism in the Apolipoprotein 1 (APOL1) gene [57]. Two APOL1 risk alleles, G1 (a missense mutation) and G2 (a frameshift deletion), have now been identified to be associated with the increased susceptibility for the development of HIVAN [57,58].

Kopp *et al.* studied the association of APOL1 genetic variation in FSGS and HIVAN [59]. Individuals who had the high-risk alleles had an OR of 29 (95% CI: 13–68) of developing HIVAN. Also, the age of onset was much earlier for G1/G2 homozygotes or compound heterozygotes. Untreated HIV-infected patients with the two APOL1 risk alleles had a 50% increased risk of developing HIVAN [59]. Furthermore, carrying the two APOL1 risk alleles alone can explain 35% of cases of HIVAN and their absence can reduce HIVAN by 67%. Recently, a G3 haplotype has been identified, but its role in the pathogenesis of HIVAN is still unclear [60].

It has been suggested that APOL1 high-risk alleles have been selected in individuals of African descent as they confer protection against trypanosomal infections. *Trypanosoma brucei rhodesiense*, the cause of human African sleeping sickness, carries a serum resistance-associated protein that binds and inactivates the wild-type APOL1, preventing this from lysing the trypansosoma. G1 and G2 allelic variants can restore the ability of human serum to lyse *T. b. rhodesiense.*

Box 2. Differential diagnosis of HIV-associated nephropathy.

- HIV-associated immune complex kidney disease
- Membranoproliferative glomerulonephritis (associated with concurrent hepatitis C infection)
- Amyloidosis
- Minimal change disease
- Postinfectious glomerulonephritis
- Thrombotic microangiopathy
- Diabetic nephropathy
- Immunoglobulin A nephropathy
- Membranous glomerulopathy

Clinical & pathological predictors of HIVAN

As shown in Box 3, in patients with HIV-1 infection, there are several predictors for the development of HIVAN, while others are helpful in excluding the diagnosis.

APOL-1 high-risk alleles

APOL1 high-risk variants strongly increase the susceptibility to development of HIVAN, but they do not account for all cases of this disease. In a recent study where 60 patients with biopsy-proven HIVAN were genotyped for APOL1 G1 and G2 polymorphisms, 5 patients had no identified risk alleles [61]. A total of 37 patients had 2 risk alleles and 18 were

Box 3. Predictors of HIV-associated nephropathy.

Genetic/clinical positive predictors of HIV-associated nephropathy

- Black Race [56]
- G1/G2 high-risk alleles for Apolipoprotein 1 [57]
- CD 4 count less than 200/ml [40]
- Proteinuria greater than 3 g/24 h [65]
- GFR between 0 and 14 ml/min [42]
- Higher echogenicity on renal ultrasound [67]

Genetic/clinical negative predictors of HIV-associated nephropathy

- Caucasian race
- No high-risk alleles for Apolipoprotein 1 [61]
- GFR >90 ml/min [42]
- Normal echogenicity on renal ultrasound [67]
- HIV-1 RNA less than 400 copies/ml [64]
- HIV-1 proviral DNA level of <10 copies/10^5 peripheral blood mononuclear cells [45]

GFR: Glomerular filtration rate.

heterozygotes. There was no difference in the pathological characteristics based on the number of risk alleles, and the risk of progression to ESRD or death was also independent of the number of risk alleles (renal survival was 9.3 months with zero or one risk allele and 11.7 months in patients with both risk alleles). Therefore, other genetic, environmental or viral factors may be contributing to the development of this disease and its progression [61,62].

Low CD4 count

Advanced HIV-1 infection is often found in patients with HIVAN. Approximately 80–90% of patients who present with HIVAN have a CD4-positive T cell count less than 200 cells/mm^3 based on the results of two studies [55,63]. In another study of 57 patients with biopsy-proven HIVAN, the mean CD4 count was 127 cells/mm^3 and the mean HIV-1 viral load was greater than 30,000 copies/ml [56].

Viral load

The average HIV-1 viral load in patients with HIVAN is greater than 30,000 copies/ml [56]. HIV-1 RNA levels can help in predicting the likelihood of a patient having HIVAN. In a study of 86 patients by Estrella *et al.*, a viral load of ≥400 copies/ml was strongly associated with HIVAN based on univariate analysis (OR: 15.5; p = 0.09). An HIV-1 RNA level of ≥400 copies/ml was highly sensitive (95.8%) but lacked specificity (35.5%) for the diagnosis of HIVAN [64]. Thus, a viral load of <400 copies/ml in the absence of clinical features of HIVAN can be used to rule out the disease [64].

Similar results were demonstrated in a study of 100 patients with HIV-1 and kidney disease; of whom 25 had biopsy-proven HIVAN [45]. In addition to measuring plasma HIV-1 RNA levels, HIV-1 proviral DNA level was measured in peripheral blood mononuclear cells and levels <10 copies/10^5 peripheral blood mononuclear cells had a negative predictive value of 100 and 100% sensitivity for the diagnosis of HIVAN [45].

Proteinuria

Proteinuria is a common finding in patients with HIVAN. In the study by Bige *et al.*, of 57 biopsy-proven HIVAN patients, mean proteinuria was 4.1 g/day [56]. Based on results of 55 biopsied patients, Atta *et al.* established that the sensitivity, specificity, positive and negative predictive values of using nephrotic range proteinuria as a noninvasive indicator of HIVAN were 73, 61, 53 and 79%, respectively [65]. Microalbuminuria has been reported in one study of HIV-1-infected patients with biopsy-proven HIVAN [66]. On the basis of these results, it can be concluded that the diagnosis of HIVAN cannot be made clinically just on the basis of the degree of proteinuria.

Renal function at the time of diagnosis

Higher serum creatinine at the time of presentation in an HIV-infected patient is associated with a diagnosis of HIVAN. In a study of 87 HIV-infected patients, the mean serum creatinine in patients with HIVAN was 7.6 mg/dl compared with 2.5 mg/dl in patients without HIVAN ($p \leq 0.0001$) [67]. Conversely, Berliner *et al.* observed that a higher GFR is a strong negative predictor for the diagnosis of HIVAN (p = 0.001) [42].

Renal echogenicity on ultrasound

Enlarged kidneys and increased cortical echogenicity have been reported in patients with HIVAN [68,69]. In a study of 76 HIV-infected patients who underwent a renal ultrasound, 20% had enlarged kidneys (defined as a kidney size >13 cm) and 89% had increased echogenicity [70]. The correlation of these radiologic findings with the pathological diagnosis of HIVAN was investigated in a cross-sectional study of 87 HIV-positive patients who underwent both a renal biopsy and a renal sonogram [67]. In this study, kidney size was demonstrated to have no association with the presence of HIVAN. However, the highest level of echogenicity based on a standardized measure was a strong predictor of HIVAN (positive likelihood ratio was 7.4; p = 0.006) [67].

Pathological findings

HIVAN is pathologically characterized by collapsing form of segmental sclerosis, epithelial cell hypertrophy, prominent tubular microcysts, focal tubular degenerative features, numerous tubuloreticular inclusions and tubulointerstitial inflammation [71–73]. Although the combination of these pathological findings is considered pathognomonic of HIVAN, the majority of these can also be observed in other diseases that can induce renal collapsing lesions such as parvovirus B 19 infection, leishmaniasis, cytomegalovirus infection, lupus nephritis and IgA nephropathy [74–78]. The use of bisphosphonates has also been linked to the

collapsing form of focal segmental glomerulosclerosis on a renal biopsy [79].

Management

There are no randomized control trials that address the management of HIVAN, and no future ones are expected. Most of the treatment options including cART, inhibition of renin–angiotensin–aldosterone system and corticosteroids are based on retrospective studies and small nonrandomized trials.

Combined active antiretroviral therapy

HIVAN generally affects patients with advanced HIV-1 infection who would require treatment of HIV-1, regardless of renal involvement. This makes it difficult to perform randomized control trials to evaluate the efficacy of cART in this population. Given the evidence of direct viral replication in renal epithelial cells in HIVAN, it seems logical that cART would be helpful in the treatment. In a retrospective cohort of 36 patients, renal survival was significantly better in the 26 patients receiving cART (adjusted hazard ratio = 0.30; 95% CI: 0.09–0.98; $p < 0.05$) compared with patient who received no treatment [80]. In addition to treatment, cART is also helpful in preventing the development of HIVAN as was shown in a cohort of 4000 HIV-infected patients followed at the Johns Hopkins Hospital [39]. The risk of HIVAN was 6.8 and 26.4 episodes per 1000 patient-years in the subgroup with AIDS in patients who did and did not receive cART, respectively. Similarly, Fabian *et al.* demonstrated that cART therapy was associated with improvement in GFR and decreased proteinuria in patients with biopsy-proven HIVAN [81].

Angiotensin converting enzyme inhibitors & angiotensin receptor blockers

Multiple studies have demonstrated the efficacy of Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in CKD [82,83]. The protective effects are largely due to decreased intraglomerular pressure, decrease in inflammatory mediators and reduction in proteinuria [84]. There is very little data about the use of these agents in patients with HIVAN. Kimmel *et al.* studied 18 patients with biopsy-proven HIVAN of whom 9 patients were treated with captopril and the rest served as controls [85]. Renal survival was enhanced in patients treated with captopril compared with the controls (mean renal survival, 156 ± 71 days vs 37 ± 5 days, respectively; $p < 0.002$). A more recent study of 44 patients with HIVAN of whom 28 were treated with fosinopril 10 mg/day found that the risk of renal failure was reduced with ACE inhibitor treatment (relative risk: 0.003; $p < 0.0001$) [86]. Therefore, in the absence of contraindications, patients with HIVAN should be considered for ACE inhibitor or ARB therapy.

Corticosteroids

The rationale for using steroids in patients with HIVAN comes from the observation that there is significant tubulointerstitial inflammation on renal biopsy in these patients. After therapy with steroids, this inflammation has been demonstrated to substantially improve [87]. However, there are no large randomized controlled trials to support steroid use in this population. Their use has been supported by uncontrolled, nonrandomized retrospective analyses. In a study of 19 patients with HIVAN treated with steroid, 2 patients progressed to ESRD within 4–5 weeks, while in the other 17 patients, serum creatinine levels decreased from 8.1 to 3.0 mg/dl ($p < 0.001$) [88].

Eustace *et al.* noted similar results in a retrospective cohort study of 21 patients of which 13 patients had received corticosteroids [89]. The relative risk for progressive azotemia with corticosteroid treatment at 3 months was 0.20 ($p < 0.05$). This association remained significant despite adjustment in separate logistical regression analyses for baseline creatinine, 24-h proteinuria, CD4 count and history of intravenous drug use, hepatitis B and hepatitis C. There were 18 infections in corticosteroid-treated patients and 8 in the noncorticosteroid-treated group. This was explained by the longer follow-up period in the corticosteroid-treated patients because of their longer renal survival compared with the untreated patients (46.6 vs 18.2 patient months).

In summary, although the use of corticosteroids is not without risk, a trial of prednisone at a starting dose of 1 mg/kg followed by a taper over 2 months is warranted in patients with HIVAN and deteriorating renal function.

Renal replacement therapy in HIVAN

Despite treatment, HIVAN often progresses to ESRD requiring the need for renal replacement therapy. Based on The United States Renal Data System data, 800–900 new cases of ESRD are attributed to HIVAN each year although most of the data are based on clinical diagnosis [90]. While the incidence of HIVAN as a cause of ESRD has remained stable, the overall prevalence has risen given increased patients' survival [90]. Although long-term survival is possible in patients with HIVAN on hemodialysis, their overall survival is worse compared with the general ESRD population potentially due to the increased rates of infection [91,92]. It has been demonstrated that the rate of infection and thrombosis is higher in HIV-1-infected patients with ESRD and arteriovenous grafts but not with arteriovenous fistulae [93–95]. However, it is important to note that the increased infection rate may be confounded by the higher number of intravenous drug use in the HIV-1-infected group.

HIV transmission in dialysis can be avoided by adherence to standard infection control procedure. Despite outbreaks of patient-to-patient HIV transmission in Argentina, Colombia and Egypt, patient-to-patient transmission has not been documented in the USA [96–99]. Given the low likelihood of patient-to-patient transmission, the CDC does not recommend routine isolation or dedicated machines for HIV-infected patients [100].

In patients on chronic peritoneal dialysis, the mean survival time for patients with HIV-1 with ESRD is lower than the non-HIV-1-infected population with a higher rate of fungal and pseudomonal peritonitis in HIV-1-infected patients [101–103].

Transplantation

HIV-1-infected patients who undergo renal transplant have excellent outcomes [104,105]. A recent prospective nonrandomized trial examined outcomes of kidney transplantation in 150 recipients who had $CD4^+$ T cell counts of at least 200/mm^3 and undetectable HIV-1 RNA levels [106]. Patients were followed for a median of 1.7 years, and patient survival at 1 and 3 years was 95 and 88% with allograft survival of 90 and 74%, respectively. The rate of rejection was higher in these patients with 1- and 3-year rejection rates of 31 and 41%, respectively, compared with a 1-year rejection rate of 12% as reported by US Scientific Registry of Transplant Recipients for the general transplant population. One explanation was that almost one-third of the enrolled patients received calcineurin inhibitors less frequently than is generally prescribed because of drug–drug interaction of the protease inhibitors (potent inhibitors of the cytochrome p-450 system) and calcineurin inhibitors. Although the measured trough levels of calcineurin inhibitors were therapeutic, the total exposure might have been subtherapeutic in these patients. Switching to integrase inhibitors may be helpful in such cases as they do not inhibit the P-450 system.

Conclusion

HIVAN is an aggressive renal disorder in patients with HIV-1 infection that affects patients of African ancestry. Although clinical predictors like low CD-4 count, high viral RNA levels, presence of high-grade proteinuria and renal echogenicity on ultrasound are helpful in making HIVAN a more likely diagnosis, confirmation by biopsy remains necessary, and the procedure is generally well tolerated in the HIV-1-infected population [107].

Expert commentary

HIVAN was the most common renal manifestation reported in HIV-1-infected individuals in the mid-1990s. With the advent of cART in Western countries, diabetes, hypertension, medication-induced nephrotoxicity and HIVICK have emerged as major etiologies of renal disease in this population. In patients with HIVAN, gene-wide association studies have demonstrated a strong link of this disorder with two coding sequence variants in the APOL1 gene confined to chromosome 22. Clinically, HIVAN is almost an exclusive disorder of individuals of African ancestry, presents in patients with uncontrolled HIV-1 infection with low CD4 count and a high HIV-1 viral load. Those patients are more likely to have high-grade proteinuria, rapid deterioration of renal function and increased echogenicity on renal ultrasound. None of these clinical features is pathognomonic of HIVAN. Conversely, the absence of these features, particularly black race, is more helpful in excluding the diagnosis. Initiating cART is the cornerstone of therapy in patients with HIVAN and has been demonstrated to cause decreased proteinuria and stabilization of renal function. In patients with significant interstitial inflammation, a trial of steroids is recommended. Treatment options of supportive nature include the use of ACE inhibitors or ARBs. In cases of progression to ESRD, renal replacement therapy with all dialysis modalities should be offered to these patients. In addition, renal transplantation is now an excellent option for select patients if HIV-1 infection is under good control.

Five-year view

Although HIVAN is rapidly declining in Western countries, the prevalence of kidney disease in HIV-1-infected individuals is increasing and is expected to increase further as a result of aging population and improved patients' survival. Consequently, the spectrum of kidney disease in this population will be primarily driven by metabolic risk factors such as obesity, diabetes and hypertension in addition to hepatitis C coinfection and the use of medications with nephrotoxic potential. As the number of patients with HIV-1 infection undergoing renal transplant increases, further studies with a longer follow-up period to address specific post-transplant issues that pertain to drug–drug interactions, infection and malignancy risk are vital in this population.

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Key issues

- In Western countries, HIV-associated nephropathy (HIVAN) remains an important cause of kidney disease in HIV-1-infected patients, but the incidence of HIV-1-associated immune complex kidney disease in this population is increasing surpassing HIVAN.
- Apolipoprotein 1 high-risk alleles have a strong association with HIVAN and their absence can eliminate its development by 67%
- Although certain clinical findings are of predictive value in the diagnosis of HIVAN, renal biopsy remains the gold standard for an accurate diagnosis.
- Initiating combined active antiretroviral therapy is vital in the prevention of HIVAN is key in its treatment along with adjunctive agents such as steroids, ACE inhibitors and angiotensin receptor blockers.

Patients who progress to ESRD should be considered candidates for kidney transplantation.

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