HIV INFECTION AND THE KIDNEY

June Fabian, *MB ChB, FCP (SA), Cert Neph*
Saraladevi Naicker, *MB ChB, FRCP, PhD*
Division of Nephrology, Department of Medicine, Johannesburg Hospital, Faculty of Health Sciences, University of the Witwatersrand

There is a wide clinical spectrum of renal disease in the course of HIV infection, which includes potentially reversible acute renal failure (ARF) (more recently known as acute kidney injury), electrolyte and acid-base disturbances, and intrinsic renal disease unrelated to HIV itself (e.g. co-morbid diabetes mellitus and hypertension).[1,2] In addition, there is the group of HIV-associated glomerulonephropathies that may present with acute or chronic renal failure. Histologically, this group is divided into the 'classic' HIV-associated nephropathy (HIVAN) with focal segmental glomerulosclerosis (HIV-FGS), HIV-associated immune complex disease (HIV-IC), and HIV-associated thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (HIV-TTP/HUS).[3] It is this group that is primarily implicated in the burden of chronic kidney disease (CKD) in the HIV-infected population.

ACUTE RENAL FAILURE

The causes of ARF in hospitalised HIV-infected patients may be community- or hospital-acquired. The latter group is 5 - 10 times more common, with worse outcomes.[4] The known causes of ARF are similar to non-HIV patients, with the most common being acute tubular necrosis (ATN) secondary to sepsis, hypotension, dehydration and nephrotoxins (Table I).[3-6] Although potentially reversible with appropriate medical therapy and dialysis, ARF carries a high mortality in this population.[5] Biopsy studies have confirmed a wide range of aetiologies.[5,7,8] In one study of hospitalised patients with HIV infection, ARF occurred in up to 20% of cases.[2] In another study, the short-term prognosis in this group of patients showed 18% mortality at 2 months, with 80% of patients diagnosed with AIDS at the time of hospital admission.[9] Since the advent of antiretroviral therapy (ART), a recent prospective study on ARF in ambulatory HIV-infected outpatients with access to ART concluded that more severe immuno-suppression (CD4 <200/µl and/or HIV-1 RNA level >10 000 copies/ml) is the predominant risk factor for ARF.[10]

ELECTROLYTE AND ACID-BASE DISORDERS

Numerous electrolyte and acid-base abnormalities have been documented with HIV infection (Table II). Abnormalities may arise either from HIV infection, opportunistic infections and malignancies associated with advanced immunosuppression, or with the many drugs that are used to treat HIV-1 and its complications.

GLOMERULAR DISEASE

The first series of autopsy reports to confirm renal disease in HIV-infected patients with clinically advanced disease showed a broad spectrum of lesions that include ATN, interstitial nephritis, nephrocalcinosis, minimal change, mesangial proliferation/hyperplasia and focal glomerulosclerosis (FGS).[14-17] Reports then began to appear in the literature describing various glomerulopathies, the most common of which was FGS. The distinguishing feature of the 'classic' glomerular lesion in HIV was collapse of the glomerular tuft – so-called 'collapsing glomerulopathy'.[5,7,14,18] Potential mechanisms of glomerular injury in HIV are depicted in Table III.

The wide spectrum of glomerulopathies with HIV infection, based on biopsy studies, can be categorised as follows:[3,19]

1. HIV-FGS ('classic' HIVAN)
2. HIV-IC: This group may have hepatitis B or C co-infection. The following patterns have been described:
   - Mesangial proliferative
   - Membranoproliferative (type I and III), lupus-like
   - Exudative-proliferative and crescentic IgA
   - Membranous
3. Various glomerulonephropathies: This is a heterogeneous group with different aetiologies:
   - Minimal change
   - Immunotactoid
   - Amyloidosis
   - Co-morbid disease: Diabetic nephropathy, hypertensive nephrosclerosis
4. HIV-TTP/HUS

European and American-based biopsy studies reveal varying frequencies of the different histological patterns described above where HIVAN is by far the most common. There have been studies documenting patterns of renal involvement in South Africa. A predominantly outpatient screening study was conducted at King Edward Hospital in Durban which is only one of a handful of studies that have evaluated the prevalence (and significance) of microalbuminuria in the HIV-infected population, as a marker of early renal disease. Thirty renal biopsies were performed (7 for persistent microalbuminuria, 23 for overt proteinuria); biopsy results appear in Table IV.[20] A study of inpatients at Chris Hani Baragwanath Hospital showed that HIV-IC was relatively

TABLE I. COMMON CAUSES (BOTH HIV- AND NON-HIV-RELATED) OF ARF IN THE HIV-INFECTED PATIENT

Pre-renal

Haemodynamic compromise from hypovolaemia (most commonly dehydration), sepsis, liver failure, heart failure, pancreatitis, non-steroidal anti-inflammatory agents (NSAIDs)

Intrarenal

- **Acute tubular necrosis (ATN)**

Sepsis, ischaemia, toxins (including traditional medication), rhabdomyolysis, hypotension, amphotericin B, pentamidine, aminoglycosides, tenofovir, NSAIDs, chemotherapy, radio contrast media

- **Renal infection**

Bacteria: micro/abscesses, pyelonephritis, mycoplasma, nocardia
Mycobacteria: tuberculosis and mycobacteria other than tuberculosis
Viruses: herpes, cytomegalovirus, varicella zoster virus, parvovirus
Fungi: aspergillus, cryptococcus, histoplasma, candida, mucormycosis
Parasites: pneumocystis, toxoplasma, microsporidia

- **Glomerulopathies**

HIV-associated nephropathy (HIVAN)/HIV-associated immune complex disease (HIV-IC)*
Other glomerulopathies: e.g. IgA, acute post-infectious glomerulonephritis (GN), lupus nephritis, crescentic glomerulonephritis (rifampicin)†
Haemolytic uraemic syndrome/thrombotic microangiopathy (HUS/TTP)
Rhabdomyolysis

- **Acute interstitial nephritis**

NSAIDs, rifampicin, indinavir, trimethoprim-sulphamethoxazole, atazanavir, immune restoration inflammatory syndrome (IRIS)‡

- **Tumours**

Renal cell carcinoma, multiple myeloma, lymphoma, Kaposi's sarcoma

Post-renal

Obstruction – crystalluria from high-dose trimethoprim-sulphamethoxazole or acyclovir, nephrolithiasis due to indinavir/atazanavir, herpes-related neurogenic bladder, hyperuricosuria from chemotherapy for haematological malignancies, retroperitoneal fibrosis

*Both HIVAN and HIV-IC are considered part of chronic renal disease but may present as a component of ARF if patients develop acute-on-chronic renal failure.

†Isolated case report of crescentic glomerulonephritis with rifampicin for TB.[11]

‡Isolated case reports of acute renal failure with tuberculous immune reconstitution syndrome which showed acute interstitial nephritis on histology.[12]

more common (21%), with HIVAN comprising 27% of biopsies (Table IV).[21] This contrasted with the histological patterns from black populations in the USA, where up to 60% of renal biopsies show HIVAN. When comparing the data from the Chris Hani Baragwanath and King Edward hospital cohorts, the data for those with overt proteinuria from Durban (there were no patients with microalbuminuria in the Chris Hani Baragwanath cohort) are contradictory. Possible explanations may be population demographics: the Chris Hani cohort comprised symptomatic inpatients with advanced renal failure, many of whom required dialysis. This was in contrast to the King Edward cohort where most of those screened were outpatients with relatively normal renal function, presumed to be at earlier stages of renal disease.

Very few data exist on screening asymptomatic HIV-infected patients for early renal disease, especially in Africa. In a Kenyan study, 216 antiretroviral-naïve patients were screened for renal disease, with an average CD4 count of 383 cells/µl.[22] Twenty-five per cent had creatinine clearance (Cr Cl) <90 ml/min, 2% had Cr Cl <60 ml/min, and 8% had proteinuria of >1 gram/day. A Ugandan study involved 229 patients with World Health Organization (WHO) clinical stage 3 disease, and CD4 counts were not done; they showed a startling prevalence of renal disease, with a Cr Cl of <80 ml/min in 48.5% of patients.[23] Screening showed that 20% had proteinuria >100 mg/dl, and 44.1% had leucocyturia on microscopy, suggestive of infection, but confirmatory cultures were not done.[23] Biopsies were not done in either study to confirm the cause of renal dysfunction or proteinuria.

The significance of microalbuminuria in HIV-1-infected patients is as yet undefined. A recent study showed a five-fold increase in the prevalence of microalbuminuria in HIV-infected individuals compared with HIV-negative controls.[24] Microalbuminuria was associated with lower CD4 counts, and the microalbuminuric group had an increased association with known cardiovascular risk factors: insulin resistance, systolic hypertension, and a family history of hypertension. Whether this translates into an increased risk of cardiovascular and renal disease remains to be determined.

The numerous glomerular lesions seen in HIV-1 infection underlie the importance of renal biopsy in the management of HIV-1-infected patients with renal disease. Evidence from numerous small studies and case reports has shown that pharmacological interventions for HIVAN (less so for other glomerular lesions) delay the progression or, in some cases, induce reversal of renal disease.[25-28]

HIV-ASSOCIATED NEPHROPATHY (HIVAN)

An association between HIV and renal disease was first reported in 1984 by investigators in New York City and Miami.[15,29,30] These groups described HIV-infected individuals with nephrotic-range proteinuria and progression to end-stage renal disease (ESRD) within 8 - 16 weeks. Mortality in these patients approached 100% within 6 months of diagnosis. During the next several years, the existence of a specific HIV-associated nephropathy (HIVAN) was confirmed as a distinct clinicopathological entity.[16,31-33] HIVAN was initially thought to be associated with AIDS but it was later

TABLE II. ELECTROLYTE AND ACID-BASE DISORDERS ASSOCIATED WITH HIV-1 INFECTION AND ITS TREATMENT

Electrolyte complications of drugs used to treat HIV/AIDS and common complications

Hypernatraemia: rifampicin, amphotericin B, foscarnet
Hyperkalaemia: ketoconazole, trimethoprim
Hypokalaemia: rifampicin, amphotericin B, didanosine, foscarnet, tenofovir
Hypomagnesaemia: mphotericin B, pentamidine
Hypocalcaemia: didanosine, pentamidine, foscarnet
Hypouricaemia: rifampicin, tenofovir
Hyperuricaemia: didanosine, pyrazinamide, ethambutol
Renal tubular acidosis: amphotericin B, trimethoprim, rifampicin, nucleotide-reverse transcriptase inhibitors (NRTIs), foscarnet, cidofovir, Fanconi syndrome with tenofovir

Sodium disorders

Low sodium (most significant)*
Hypovolaemia, renal tubular salt-wasting, adrenal insufficiency, syndrome of inappropriate ADH secretion (SIADH), haemodilution – usually owing to replacement with inappropriate fluids

Potassium disorders

Low potassium
Gastrointestinal losses: by far the most common cause
Renal losses: drugs: amphotericin B, Fanconi syndrome with tenofovir

High potassium
Adrenal insufficiency, acute or chronic kidney disease with tubular damage, drugs (commonly, co-trimoxazole)

Acid-base disorders

Normal anion gap metabolic acidosis
Diarrhoea, adrenal insufficiency, renal tubular acidosis (amphotericin B, tenofovir)

Raised anion gap metabolic acidosis
Type A lactic acidosis (more common than type B): tissue hypoxia most commonly from protracted hypotension and/or hypovolaemia, sepsis, diabetic keto-acidosis
Type B lactic acidosis: drug-induced mitochondrial toxicity due to zidovudine, didanosine, lamivudine, stavudine, zalcitabine

*Hyponatraemia is relatively common in both HIV-infected in- and outpatients. In hospitalised HIV-infected patients, hyponatraemia has been associated with advanced immunosuppression and increased mortality.[13]

TABLE III. MECHANISMS OF GLOMERULAR INJURY INDUCED BY HIV INFECTION

- **Circulating immune complexes involving:**
  Viral antigens and host antiviral antibodies
  Endogenous antigens modified by viral injury and host auto-antibodies
- ***In situ* immune-mediated mechanisms involving:**
  Viral antigens bound to glomerular structures
- **Expression of viral proteins or pathogenic pro-inflammatory factors in tissue inducing the following reactions:**
  Cell death through necrosis/apoptosis/cellular dysfunction
  Increased matrix synthesis and/or decreased matrix degradation
  Release of cytokines, chemokines, adhesion molecules, growth factors
- **Direct cytopathogenic effect on glomerular cells with undefined mechanisms**
- **Tubulointerstitial injuries due to direct cytopathogenic effects, and secondary mediators released in response to glomerular inflammation**
- **Haemodynamic disturbance, multiorgan failure**
- **Complicating rhabdomyolysis, hepatorenal syndrome**
- **Nephrotoxicity of antiviral therapy (occasional)**

recognised that the lesion can occur at any stage of HIV infection, even prior to antibody seroconversion.[34] Most of the literature report that patients with HIVAN present late in the course of their HIV infection with advanced renal failure. This late detection of HIVAN could be the result of a lack of screening HIV-infected patients for proteinuria and/or renal dysfunction. The relative absence of peripheral oedema and hypertension in those with HIVAN may also delay diagnosis. The outcome of patients with HIVAN has been correlated with the clinical stage of their disease, suggesting that survival improves with earlier detection.[35] Regarding the significance of renal dysfunction and proteinuria in the HIV-infected population, studies have shown an increased relative risk of 2.5 - 3.0 for overall mortality, after correcting for other risk factors.[36,37] Of interest in one study was that 77% of renal abnormalities developed with CD4 counts above 200 cells/µl.[37] This was also seen in the study from Durban where the mean CD4 count of those with biopsy-proven HIVAN was 232 cells/µl.[3,20] Symptomatic HIVAN is now classified as clinical stage 4 disease by the WHO.[38]

EPIDEMIOLOGY AND RACIAL PREDILECTION OF HIVAN

There is a marked racial predilection for the development of HIVAN – over 90% of patients are black.[1,14,35,39-41] This has been confirmed in paediatric studies.[33] Studies from African countries regarding the susceptibility of Africans to HIVAN are scanty. The reasons for the racial predilection of HIVAN are

TABLE IV. HIV-INFECTED PATIENTS BIOPSIED IN SOUTH AFRICA[20, 21]

Histological lesion on renal biopsy	Percentage of total biopsies (King Edward study)	Percentage of total biopsies (Chris Hani Baragwanath study)
HIVAN	70%	27%
HIV-IC	-	21%
Membranous nephropathy	13.3% (all with HIVAN)	13%
Other non-glomerulonephritic renal diseases	-	10%
Other glomerulonephritides	-	9%
Post-infectious glomerulonephritis	-	8%
Mesangioproliferative glomerulonephritis	-	6%
IgA nephropathy	-	5%
Membranoproliferative glomerulonephritis	6.6%	-
Interstitial nephritis	10.1%	-

TABLE V. CURRENT RECOMMENDATIONS FOR MANAGEMENT OF HIVAN

ART	Triple therapy: dose adjusted for renal failure (see Table VI)
ACE-I or A2RB	If proteinuria >1 g/24 hours or if proteinuria on diptsick persists after 3 months on ART
Corticosteroids	After consultation with a nephrologist
Chronic renal failure (follow up 3-monthly)	Refer to a nephrologist if possible, manage as for any patient with chronic renal failure: Hypertension (aim for BP <120/70 mmHg) Calcium/phosphate/potassium metabolism Anaemia (especially if using AZT/3TC) Acidosis Dyslipidaemia Dietary recommendations
End-stage renal disease	Initiate renal replacement therapy or refer to nephrologist if therapy unavailable

TABLE VI. DOSE ADJUSTMENT FOR COMMONLY-USED NNRTI*

Agent	Normal dose	Estimated GFR (creatinine clearance: Cr Cl)
Zidovudine	300 mg bd po	10 - 50 ml/min = 200 mg tds <10 ml/min = 100 mg tds po
Lamivudine	150 mg bd po	30 - 49 ml/min = 150 mg daily po 15 - 29 ml/min = 100 mg daily po 5 - 14 ml/min = 50 mg daily po <5 ml/min = 25 mg daily po
Stavudine	30 mg bd po	26 - 50 ml/min = 15 mg bd po <26 ml/min = 15 mg daily po
Didanosine	>60 kg: 200 mg bd po	30 - 59 ml/min = 200 mg daily po 10 - 29 ml/min = 150 mg daily po <10 ml/min = 100 mg daily po
	<60 kg 125 mg bd po	30 - 59 ml/min = 150 mg daily po 10 - 29 ml/min = 100 mg daily po <10 ml/min = 75 mg daily po
Tenofovir	300 mg daily po	30 - 49 ml/min = 300 mg every second day 10 - 29 ml/min = 300 mg every third day <10 ml/min = 300 mg once-weekly

*No dose adjustment necessary for abacavir; protease inhibitors, nevirapine, delavirine and efavirenz are all metabolised by liver and dose adjustment is not indicated.

unexplained. Some have postulated a genetic predisposition, but candidate genes have not been identified.[14,39] Studies involving the HIV transgenic mouse, bearing the *gag-pol*-deleted HIV transgene, have provided valuable insight into the genetic determinants of renal disease. This strain of mouse develops renal disease very similar to HIVAN in humans, but when these mice are bred onto various other genetic backgrounds, the phenotypic expression of renal disease differs greatly.[3] One study has shown that there appears to be a strong familial clustering of ESRD among blacks commencing renal replacement therapy due to HIVAN.[41] This clustering appears to be independent of HIV infection *per se*. In most cases, the affected relatives had ESRD due to hypertension or diabetes. HIVAN also appears to follow a more severe clinical course in black patients.[42] Studies in black patients have shown a higher prevalence of both severe glomerular lesions (focal glomerulosclerosis) and nephrotic-range proteinuria with renal dysfunction in the presence of normo-hypotension.[1,40,42]

In the 1980s, HIVAN was an uncommon cause of ESRD in the USA.[43] This was partly due to the high mortality in this group and the absence of ART. With improved survival after the introduction of ART, HIVAN became the most rapidly increasing cause of ESRD in the USA by 1990.[43] In 1995, although the decline in mortality from AIDS was dramatic, the number of new cases of ESRD due to HIVAN did not decline.[43] Instead, mortality data have shown a steady plateau in the Afro-American population, the population at highest risk for HIVAN in the USA.[43-45] In 2004, HIVAN was the seventh leading cause of ESRD in Afro-Americans.

Statistics in the USA estimate the incidence of HIVAN to be 3.5 - 12%.[43] If this were extrapolated to sub-Saharan Africa (with an estimated 25.8 million people infected with HIV), between 903 000 and 3.1 million people would be predicted to have HIVAN. With the advent of unrestricted access to ART, one may postulate that the epidemiological pattern of HIVAN that evolved in the USA over the last 14 years may predict what will happen in sub-Saharan Africa. This presents a potentially unprecedented burden of chronic kidney disease, given the current resources available for managing renal disease in this region. There is a critical role for local research, in the form of prospective randomised controlled trials on the impact of early diagnosis and treatment of HIVAN and its effect on outcome regarding morbidity, mortality, and prevention of progression to ESRD in sub-Saharan Africa. In addition, a national programme needs to be devised on the comprehensive management of renal disease in HIV-1 infection that addresses not only the prevention of renal disease but also the management of those with CKD, including renal replacement therapy and transplantation.

HISTOPATHOLOGY OF HIVAN

HIVAN is characterised by a specific constellation of pathological findings on biopsy that involve glomerular, tubular and interstitial compartments of the kidney (Fig. 1).[1,31,46]

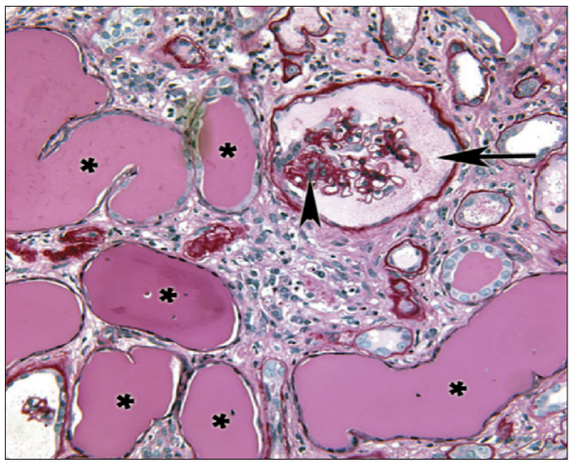

Fig. 1. Typical histopathological findings of HIVAN.[46] *Periodic acid-Schiff staining demonstrates focal segmental glomerulosclerosis (arrowhead) with collapse of the glomerular tuft (arrow), tubular microcystic disease (*), interstitial lymphocytic infiltration and interstitial fibrosis. Magnification ×200.*

MANAGEMENT OF HIVAN

The management of biopsy-proven HIVAN involves not only ART but, in those with chronic renal failure, also the same treatment that would apply for any patient with the condition. This includes referral to a nephrologist, if possible; regular follow-up; monitoring and treatment of blood pressure, potassium, calcium, phosphate and lipid metabolism; anaemia management; and appropriate dose adjustment for nephrotoxic agents including ART. In those who progress to end-stage renal failure, the initiation of renal replacement therapy – which includes dialysis (haemo/peritoneal) and renal transplantation – needs to be initiated timeously and appropriately. There have been no prospective randomised controlled studies with any form of therapy for HIVAN to date. Therapies used in the treatment of HIVAN include corticosteroids, angiotensin-converting enzyme inhibitors (ACE-I) and ART.

Corticosteroids

In various studies, patients with HIVAN treated with prednisone experienced an improvement in renal function and reduction of proteinuria, but complications such as relapse after steroid withdrawal, opportunistic infections, psychosis and gastrointestinal bleeding were relatively common.[47,48] The use of corticosteroids has become less important since the advent of ART and ACE-I treatment. The role for corticosteroids should be reserved for refractory cases of severe nephrotic syndrome already on ART and ACE-I and be administered after consultation with a nephrologist.

Angiotensin-converting enzyme inhibitors (ACE-Is)

Different ACE-Is (captopril; fosinopril) have been shown to reduce proteinuria, stabilise renal function and delay the progression of renal failure in HIVAN. Some of these studies were conducted prior to the availability of ART. The potentially beneficial effects of ACE-I may be related

to improved renal haemodynamic, reduced proteinuria or cytokine modulation (Infectious Diseases Society of America) (IDSA). The effects of ARB (angiotensin-2 receptor blockers) in the treatment of HIVAN are unknown, just as the effects of ACE-I or ARB in the treatment of HIV-associated renal disease other than HIVAN are unknown.

Highly active antiretroviral therapy (HAART)

Because HIV-1 itself appears to be the cause of HIVAN and may contribute to other renal diseases in HIV-1-infected patients (e.g. immune-complex glomerulonephritides), ART appears to be a logical choice in the management of HIV-associated renal disease. Initially, zidovudine (AZT) monotherapy was shown to be beneficial in the treatment of HIVAN.[49,50] There appears to be a more beneficial effect of ART (triple combination) over zidovudine monotherapy in the management of HIVAN.[25-28,51] In addition to being effective in treating established HIVAN, ART may decrease the actual incidence of *de novo* HIVAN.[52,53]

CONCLUSION

Renal disease in HIV infection is common, multifactorial and often challenging – for patient and clinician. If untreated or inappropriately managed, it can be fatal. It is not only essential for clinicians to be able to manage renal disease in HIV but also for them to be able to access referral institutions and nephrologists for support.

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