

Chronic kidney disease in HIV infection: early detection and preventive strategies

HIV infection raises the risk of chronic kidney disease.

JUNE FABIAN, MPharm, MB BCh, FCP (SA), Cert Neph
Division of Nephrology, University of the Witwatersrand and Johannesburg Hospital

June Fabian is a consultant in the Division of Nephrology at Johannesburg Hospital, which forms part of the Department of Medicine, University of the Witwatersrand. She is currently doing an MMed on HIV infection and renal disease at the HIV outpatient clinic at Johannesburg Hospital and has a special interest in renal disease and HIV.

SARALA NAICKER, MB ChB, MRCP (UK), FRCP (Lond), FCP (SA), PhD
Professor, Division of Nephrology, University of the Witwatersrand and Johannesburg Hospital

Sarala Naicker is the head of the Division of Nephrology at the University of the Witwatersrand. Her research interests are renal disease and HIV, prevention of chronic kidney disease and cardiovascular disease in renal patients. Her other major interest is medical education.

HIV infection and its devastating consequences have placed an enormous strain on health care resources, those living with/without HIV, their families and friends. In addition to the broad, multi-dimensional impact of this infection, when considering kidney disease, HIV has unleashed a new burden of both acute and chronic kidney disease (CKD).

Epidemiology of HIV infection

Statistical data from UNAIDS in December 2006¹ reveal the following (Fig. 1):

- The number of people living with HIV worldwide is estimated to be 39.5 million in 2006, 2.6 million more than in 2004 (Fig. 1). This includes the estimated 4.3 million newly infected adults and children. Young people (15 - 24 years of age) accounted for 40% of the new infections in 2006. Two-thirds (63%) of all adults and children with HIV worldwide live in sub-Saharan Africa (24.7 million), with the epicentre in Mozambique, Swaziland and South Africa.
- In sub-Saharan Africa 13.3 million women over the age of 15 are infected with HIV. In this region, women are more likely than men to be infected with HIV and they are more likely to be the ones caring for people infected with HIV.

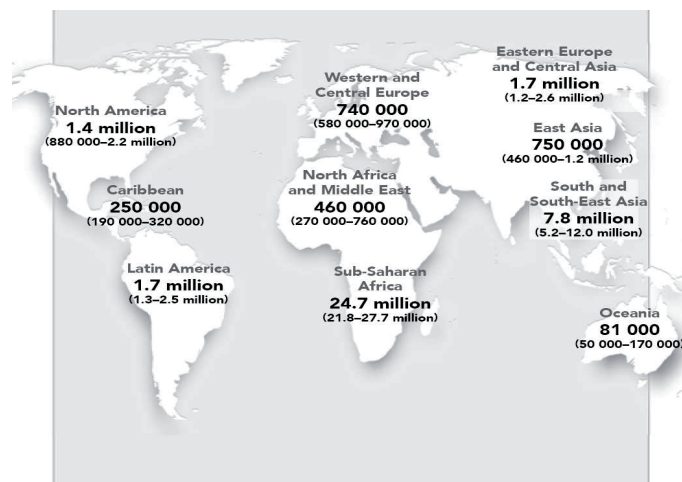


Fig. 1. Adults and children estimated to be living with HIV in 2006: 39.5 million (34.1 - 47.1) (http://www.unaids.org/en/HIV_data/epi2006/) (accessed 11 March 2007).

- Of all the known deaths worldwide due to AIDS in 2006, 72% occurred in sub-Saharan Africa (2.1 of a total of 2.7 million).
- One in 3 adults in Swaziland was living with HIV in 2005 (33%), the most intense epidemic in the world.
- South Africa, in terms of sheer numbers, has one of the world's largest HIV epidemics. Prevalence rates for HIV infection in women attending public antenatal clinics were more than one-third higher (35%) than it had been in 1999. Data collected from antenatal clinics suggest that the epidemic has not yet reached a plateau. In 2005 there were 5.5 million HIV-infected people in South Africa and 240 000 of those were children. In the age group 15 - 24 years, young women are 4 times more likely to be HIV infected than men.
- South African mortality data are now revealing the devastating impact of the epidemic. Total death rates from all causes in South Africa increased by 79% from 1997 to 2004. Death rates from natural causes for women aged 25 - 34 years have increased five-fold from 1997 to 2004. For males 30 - 44 years of age, death rates have more than doubled in the same time period.

HIV infection and the kidney

There is a wide spectrum of renal disease that occurs in the course of HIV infection. This includes:

- acute renal failure
- electrolyte and acid-base disturbances
- intrinsic renal disease unrelated to HIV itself (diabetes mellitus and hypertension)²
- HIV-associated glomerulonephropathies, which may present with either acute or chronic renal failure (Table I)³
- Side-effects related to treatment of HIV, including those due to:
 - antiretroviral therapy (tenofovir, in-dinavir)
 - drugs used to treat infectious complications of HIV (sulphamethoxazole, acyclovir)
 - long-term metabolic side-effects of antiretroviral therapy (particularly the protease inhibitors).

Table I. Spectrum of glomerular disease with HIV

Glomerular pattern	Subtypes
HIV- focal glomerulosclerosis (FGS) ('classic' HIVAN)	Some have described a mixed variant of HIV-FGS in combination with a proliferative glomerulonephritis
HIV- immune complex disease (ICD) (this group often have hepatitis B or C coinfection)	Mesangial proliferative Membranoproliferative (type I and III) Lupus-like Exudative-proliferative Crescentic IgA Membranous
Various glomerulonephropathies (this is a heterogenous group with different aetiologies)	Minimal change Immunotactoid Amyloidosis
HIV-thrombotic thrombocytopenic purpura (TTP)/HUS (thrombotic microangiopathy)	
Co-morbid disease	Diabetic nephropathy Hypertensive nephrosclerosis Auto-immune disease (e.g. lupus nephritis)

With regard to HIV-associated glomerulonephropathies, biopsy studies reveal varying frequencies of histological patterns.⁴ HIV-associated nephropathy (HIVAN) is most common, with other lesions accounting for one-quarter to one-third of the total. A biopsy study at Chris Hani Baragwanath Hospital in Soweto showed that HIVAN was present in 27% (Fig. 2).⁵

The above data are based on patients with symptomatic renal disease, who are often at more advanced stages of their illness. Two studies were recently conducted in Kenyan and Ugandan outpatient HIV clinics.^{6,7}

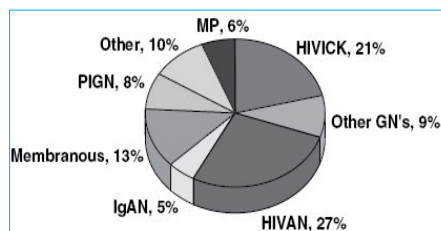


Fig. 2. HIV-positive patients biopsied between 2003 and 2004. HIVICK: immune complex deposition disease; Other GN's: other glomerulonephritides; HIVAN: collapsing glomerulopathy; IgAN: IgA nephropathy; PIGN: post-infectious glomerulonephritis; Other: other (non-glomerulonephritic) renal disease; MP: mesangial proliferative glomerulonephritis.⁵

Renal histology in HIV infection is variable and the importance of renal biopsy must be emphasised.

In Kenya, 25% of patients had creatinine clearance (Cr Cl) < 90 ml/min, 2% had Cr Cl < 60 ml/min and 8% had proteinuria of > 1 g/day.⁶ The Ugandan study showed a Cr Cl of < 80 ml/min in 48.5% of patients and 20% had proteinuria > 100 mg/dl.⁷ A study was conducted in Durban on HIV-positive patients screened for proteinuria, including microalbuminuria. This is one of a handful of studies that have evaluated the prevalence and significance of microalbuminuria as a marker of early renal disease in HIV. Han *et al.*⁸ screened 615 patients; 30 renal biopsies were performed, 7 for persistent microalbuminuria, 23 for overt proteinuria. Histology showed HIVAN in 21/30 (72.4%); HIVAN + membranous glomerulonephritis (GN) 4/30 (13.8%); membranoproliferative GN 2/30 (6.9%); interstitial nephritis 2/30 (6.9%). The prevalence of HIVAN in patients with persistent microalbuminuria was 85.7%.

With improved survival after the introduction of antiretroviral therapy, HIVAN became the most rapidly increasing cause of ESRD in the USA by 1990.

Renal histology in HIV infection is variable and the importance of renal biopsy must be emphasised. There is evidence (from numerous small studies and case reports) that pharmacological interventions for HIV focal glomerulosclerosis (FGS)/HIVAN delay the progression or prevent the onset of renal disease.⁹ In resource-limited settings, such as our own, renal biopsy is often not possible, precluding many patients from diagnosis and appropriate treatment. For these reasons, it is an attractive option to develop non-invasive ways of diagnosing HIVAN at a primary care level. Thus far, no studies have defined non-invasive criteria. Certain groups have investigated sonographic criteria as predictors of HIVAN.¹⁰ More recently, it was shown that the degree of proteinuria (> 3 g/24 h or a protein:creatinine ratio > 3) in combination with CD4 count was not predictive of HIVAN.¹¹ This is open for further research as accurate, non-invasive criteria for the diagnosis of HIVAN in resource-limited settings would be extremely valuable.

Table II. Mechanisms of glomerular injury induced by HIV-1 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 proinflammatory 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)

The stark reality at present in South Africa is that most people with ESRD and HIV die.

Pathogenesis of glomerular disease

Various mechanisms for the development of glomerular disease in HIV infection have been proposed (Table II).¹²

HIV-associated nephropathy

In the 1980s HIVAN was an uncommon cause of end-stage renal disease (ESRD) in the USA.¹³ With improved survival after the introduction of antiretroviral therapy, HIVAN became the most rapidly increasing cause of ESRD in the USA by 1990.¹³ There is a marked racial predilection for the development of HIVAN, as over 90% of patients are black, with a male predominance.² Statistics in the USA estimate the incidence of HIVAN to be 3.5 - 12%.¹³ If this were to be extrapolated to sub-Saharan Africa, between 0.9 and 3.1 million people would be predicted to have HIVAN. This presents a potentially unprecedented burden of CKD. At present, HIV-positive patients with end-stage renal failure (ESRF) are rarely offered chronic dialysis or transplantation in the public health sector of South Africa. This poses daunting logistical, financial and ethical issues for clinical nephrologists.

Histopathology of HIVAN (Fig. 3)

HIVAN is characterised by a specific constellation of pathological findings that involve glomerular, tubular and interstitial compartments of the kidney:¹⁴

- focal glomerulosclerosis with prominent collapse of the glomerular tuft
- tubular dilatation, flattening of tubular epithelial cells, microcysts
- lymphocytic infiltrates of interstitium with patchy oedema and/or interstitial fibrosis
- endothelial tubuloreticular inclusions (on electron microscopy), thought to be related to increased interferon levels, are characteristic but not pathognomic of HIVAN

- increased mesangial matrix, hyperplasia of mesangial cells may be seen but whether this is part of the spectrum of HIVAN is debatable.

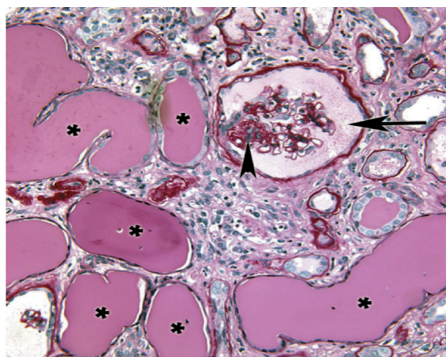


Fig. 3. Typical histopathological findings of HIVAN. Periodic acid-Schiff staining demonstrates focal segmental glomerulosclerosis (arrowhead) with collapse of the glomerular tuft (arrow), tubular microcystic disease (*), interstitial lymphocytic infiltration and interstitial fibrosis. Magnification x 200.¹³

Pharmacological treatment of HIVAN

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 those directed at the kidney damage from HIV infection, which have included corticosteroids, cyclosporine and antiretroviral therapy. The other focus of treatment involves agents for the treatment of proteinuria such as angiotensin-converting enzyme inhibitors (ACE-I), dyslipidaemias (if nephrotic), and co-morbid disease (hypertension). Renal replacement therapy (RRT) options for patients who have reached ESRD include haemo- or peritoneal dialysis and renal transplantation.

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.⁹ Because these studies have no long-term follow-up, are small in size and not randomised, no clear conclusions can be made regarding their use in HIVAN. Most clinicians would not treat biopsy-proven HIVAN with corticosteroids since the availability of antiretroviral therapy.

Angiotensin-converting enzyme inhibitors (ACE-I)

Small studies have shown benefit with ACE-I such as captopril and fosinopril.^{15,16} The

beneficial effects of ACE-I may be related to improved renal haemodynamics, reduced proteinuria or cytokine modulation.¹⁷ The effects of angiotensin-2 receptor blockers (ARBs) in the treatment of HIVAN are unknown, just as the effects of ACE-I or ARBs in the treatment of HIV-associated renal disease other than HIVAN are unknown.

Cyclosporine

The effectiveness of cyclosporine in inducing remission of proteinuria was reported in children with HIVAN.¹⁸ There are no studies evaluating the role of cyclosporine in adults with HIVAN.

Highly active antiretroviral therapy

Antiretroviral therapy appears to be a logical choice in the management of HIV-associated renal disease. There appears to be a more beneficial effect of triple combination over zidovudine monotherapy.¹⁹ Regimens containing protease inhibitors have been shown to be associated with significant slowing of the decline in creatinine clearance. Whether this effect is superior to the effect of other classes of antiretroviral therapy is unknown.¹⁹

Screening for renal disease in HIV

The extent of the HIV epidemic, its associated burden of CKD in sub-Saharan Africa, coupled with the cost of RRT in a resource-limited setting, make this a very difficult problem. The stark reality at present in South Africa is that most people with ESRD and HIV die. Some have limited access to dialysis (mostly in the private sector), and this group of patients are not offered cadaveric kidney transplantation. Currently, most clinicians deal with advanced stages of CKD in HIV, and prevention or early detection of renal disease in this population is neglected. This is partly because patients present late, but also because there has been very little research globally and in sub-Saharan Africa on the impact of interventions (e.g. antiretrovirals, ACE-I) on the progression of CKD in this population. To address this, we require local research and a firm commitment at national level as the platform from which a clear strategy for management from primary to tertiary levels of health care can be implemented. Primary health care practitioners need a working system in place for referral of patients with abnormalities on screening. Referral centres require resources for appropriate investigation and treatment of patients with confirmed CKD.

Currently, there are no guidelines in South Africa for screening of HIV-infected individuals for CKD. Urinary screening

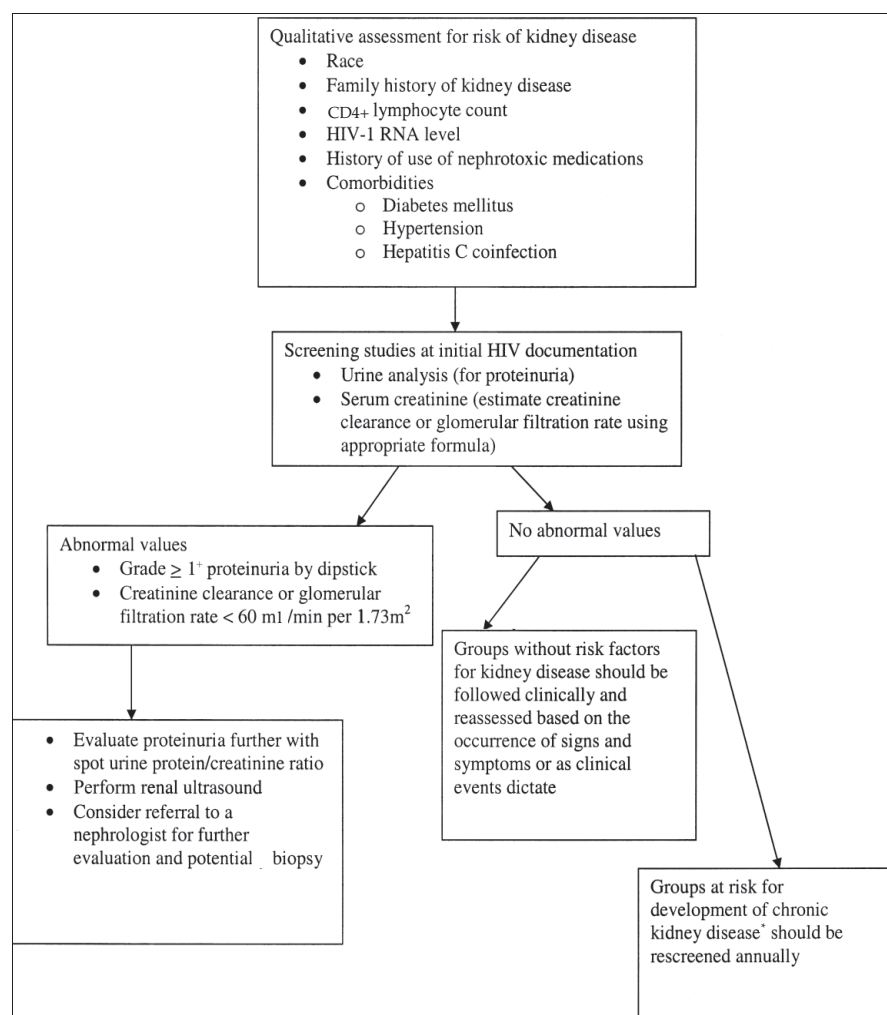


Fig. 4. Suggested screening algorithm for HIV-related renal diseases.* Groups at risk for CKD include individuals of African American race; individuals with diabetes, hypertension, or hepatitis C virus coinfection; individuals with CD4+ cell counts < 200 cells/mm³; and individuals with HIV RNA levels > 4 000 copies/ml.²⁰

of new or 'at risk' patients for the presence of renal disease in antiretroviral clinics in South Africa is unfortunately not considered standard of care. The care of patients with CKD and HIV unfortunately remains in the hands of a few interested clinicians, which is not sustainable. The Infectious Diseases Society of America (IDSA) published guidelines to this effect in 2005.²⁰ Their recommendation is that all individuals be assessed for kidney disease at the time of diagnosis of HIV infection with a screening urinalysis for proteinuria and a calculated estimate of renal function. This allows for, detection of renal disease and dose adjustment of antiretrovirals and other commonly used drugs in HIV infection, such as acyclovir, trimethoprim-sulphamethoxazole, and anti-TB medication. A screening algorithm has been suggested by the IDSA and is depicted in Fig. 4. The IDSA criteria for those at 'high risk' for development of proteinuric renal disease are: African Americans, CD4 counts < 200 cells/mm³, HIV RNA levels > 4 000 copies/ml, patients with diabetes mellitus, hypertension or hepatitis C co-infection

(although chronic hepatitis C infection is not very common in South Africa). Most patients in South African antiretroviral clinics would fulfil these criteria based on WHO staging and CD4 count. Ideally, the programme for prevention of CKD in HIV would work best if coupled to an early screening programme for HIV testing, where the shift is on diagnosing HIV in early stages of infection, when most are still asymptomatic. At present, the screening algorithm could be utilised as a template for clinicians. We would however suggest that, as a matter of urgency, a working committee be established for drawing up national guidelines for the screening, detection and management of CKD in HIV-infected individuals in South Africa.

Conclusion

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. It is proposed that a working group

for the establishment of guidelines for the screening, early detection and management of renal disease in HIV-infected individuals in South Africa is established.

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CKD and HIV

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In a nutshell

- Sub-Saharan Africa is at the epicentre of the HIV pandemic.
- Acute and chronic kidney disease is common in the course of HIV infection.
- There is a huge projected burden of CKD as a result of HIV in sub-Saharan Africa, for which we do not have the resources to cope.
- At present, most people with ESRD and HIV are not offered renal replacement therapy (dialysis and transplantation).
- More emphasis needs to be placed on screening and prevention of CKD in HIV.
- A screening and prevention programme for CKD in HIV needs to be devised and implemented as a matter of urgency.
- Appropriate and well-designed research from the sub-Saharan region needs to be done to determine the effect of interventions on the progression of CKD in HIV.



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