

HIV and renal disease in Africa: the journey so far and future directions

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Received for publication: 16/12/2010

Accepted: 23/12/2010

Key-Words:

Africa; cART; HIV; kidney disease.

INTRODUCTION

The world health organization (WHO) has estimated that 33.2 million people have been infected globally with the human immunodeficiency virus (HIV), and about 22 million of those affected come

from sub-Saharan Africa (SSA) (Figure 1)¹. Despite the large numbers of patients infected with HIV in SSA, much of our knowledge of the manifestations of this disease has originated from developed countries with fewer patients afflicted with the virus.

The major cause of the epidemic in South Africa has been the denial of the link between the virus and the disease². Mr. Thabo Mbeki (immediate past president of South Africa) was the principal culprit.

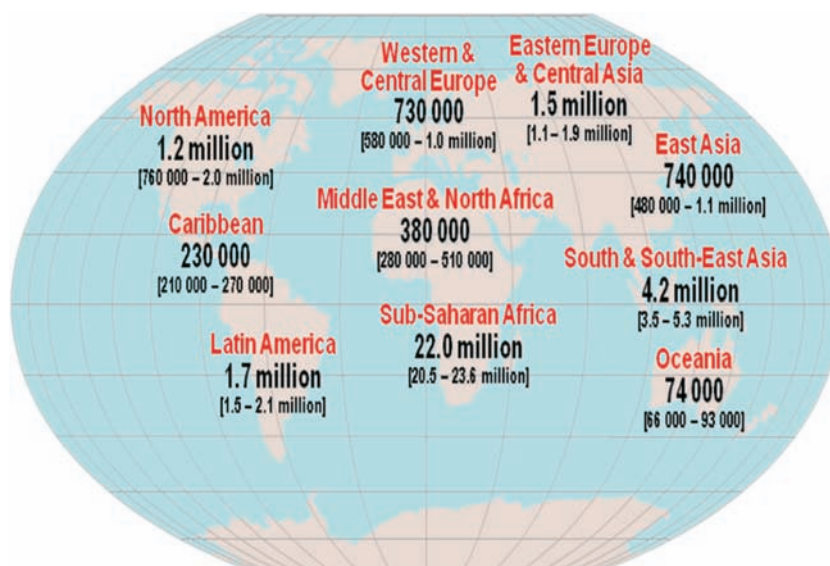


Figure 1

Adults and children estimated to be living with HIV in 2007¹

This “head-in-sand” approach caused much delay in research and treatment as well as the formulation of national or regional policies regarding HIV/AIDS. Consequently, access to basic health care facilities and combined antiretroviral therapy (cART) required for the treatment of HIV/AIDS was withheld³.

The association between kidney disease and HIV infection is clear, and the first reports of the classic and well-described HIV-associated nephropathy (HIVAN) were published in the mid-1980s. The first reports described a disease that was common in people of African descent and clinically characterized by the presence of heavy proteinuria, minimal oedema and a rapid progression to end-stage renal disease (ESRD)⁴. HIVAN is the most common disease described in biopsy series of patients with HIV infection and kidney disease^{5,6}. Studies have shown that HIV-positive patients can present with acute or chronic kidney disease related to infection with the virus⁷⁻¹⁰. HIV patients presenting with features resembling acute kidney injury and dialyzed in our institution have shown a variety of histopathological features, including acute tubular necrosis, renal tuberculosis and lymphoma of the kidney with or without HIVAN¹⁰.

Patterns of renal disease as seen in our centre are shown in Table 1, with HIVAN being the most common.

Table 1.

Biopsy-proven patterns of renal disease seen in HIV-positive patients in Cape Town (January 2000 – December 2009).

Type of renal disease	N (%)
1. HIVAN	145 (55.3)
2. Tubulo-interstitial diseases	
• Acute Tubular Necrosis	21 (8.0)
• Acute Interstitial Nephritis	11 (4.2)
• Chronic Interstitial Nephritis	2 (0.8)
3. Glomerular diseases	
• IgA Nephropathy	1 (0.4)
• Minimal change disease	2 (0.8)
• Mesangiocapillary GN	8 (3.1)
• Membranous GN	12 (4.6)
• Mesangio-proliferative GN	11 (4.2)
• Post-infectious GN	7 (2.6)
4. Others	
• Diabetic nephropathy	8 (3.1)
• Hypertensive nephrosclerosis	7 (2.6)
• Crescentic GN	6 (2.3)
• Amyloidosis	1 (0.4)
• Myeloma kidney	1 (0.4)
• End-stage kidney	19 (7.2)

We have drawn up a clinico-pathological classification which we believe will increase knowledge on outcome studies in the field of HIV nephropathy.

■ THE JOURNEY SO FAR

■ 1. The cART effect

Since the mass roll-out of cART across the continent, negative attitudes and perceptions of patients with HIV infection have improved. In one study in Uganda, the impact of cART on renal function among patients participating in a home-based AIDS care was evaluated, and it was observed that renal dysfunction improved following two years of cART¹¹. This study had a positive effect on the management of patients with HIV and renal disease as many who would ordinarily not qualify for cART (policy was to start cART if CD4 count was <200 cells/mm³), were started on treatment if they had kidney disease confirmed by biopsy or through abnormal laboratory results.

In a study, of a cohort of 25,779 HIV-positive patients in Zambia, designed to assess the association between baseline renal insufficiency and mortality among adults initiating cART, it was observed that 33.5% of patients already had renal dysfunction at initiation of the study.

There was an associated increased risk of mortality at 90 days in those with renal dysfunction compared with those without renal dysfunction at the time of initiation of therapy¹². Investigators were therefore made aware of the need for regular screening and surveillance for kidney disease (through routine monitoring of serum creatinine and urine protein excretion) in HIV-positive patients.

■ 2. Needle in the kidney – the need for more renal biopsies from Africa

Renal biopsy is undeniably one of the most important tools in the practice of clinical nephrology¹³. The tools and skills required for the performance of a renal biopsy are not readily available in several parts of Africa and nephrologists often rely on the clinical presentation of patients in order to assess renal kidney involvement. In the few centres where

renal biopsies are routinely performed, different, novel histological patterns of renal disease, associated with HIV, have been described. Gerntholtz *et al.* were the first to describe the presence of HIV-immune complex kidney disease in some patients with HIVAN and named the appearance “ball-in-cup”⁹. Although we have identified the same pattern in patients biopsied in our centre, we believe it to be a variant of post-infectious or membranous glomerulonephritis³. We have also observed other variants of glomerular disease, which our pathologist has named “central sclerosis” variant (figure 2A) and “foetal” glomeruli (figure 2B). Figure 2C is a glomerulus from a foetal kidney (included for comparison). The kidney pathology in HIV therefore is a spectrum

of disease rather than a single disease (e.g., classic HIVAN, figure 2D) as is often discussed.

As there are no large epidemiological studies in Africa with data regarding the incidence and prevalence of kidney disease, there is an overreliance on published case reports, retrospective studies and observational studies to provide information on the extent of HIV renal disease in the continent. A recent retrospective review of our overall renal biopsy database highlighted the importance of performing renal biopsies. In this review we found that incidence of secondary glomerular diseases (particularly HIVAN) was observed to be on the rise. We observed a four-fold increase in biopsies performed for HIVAN from

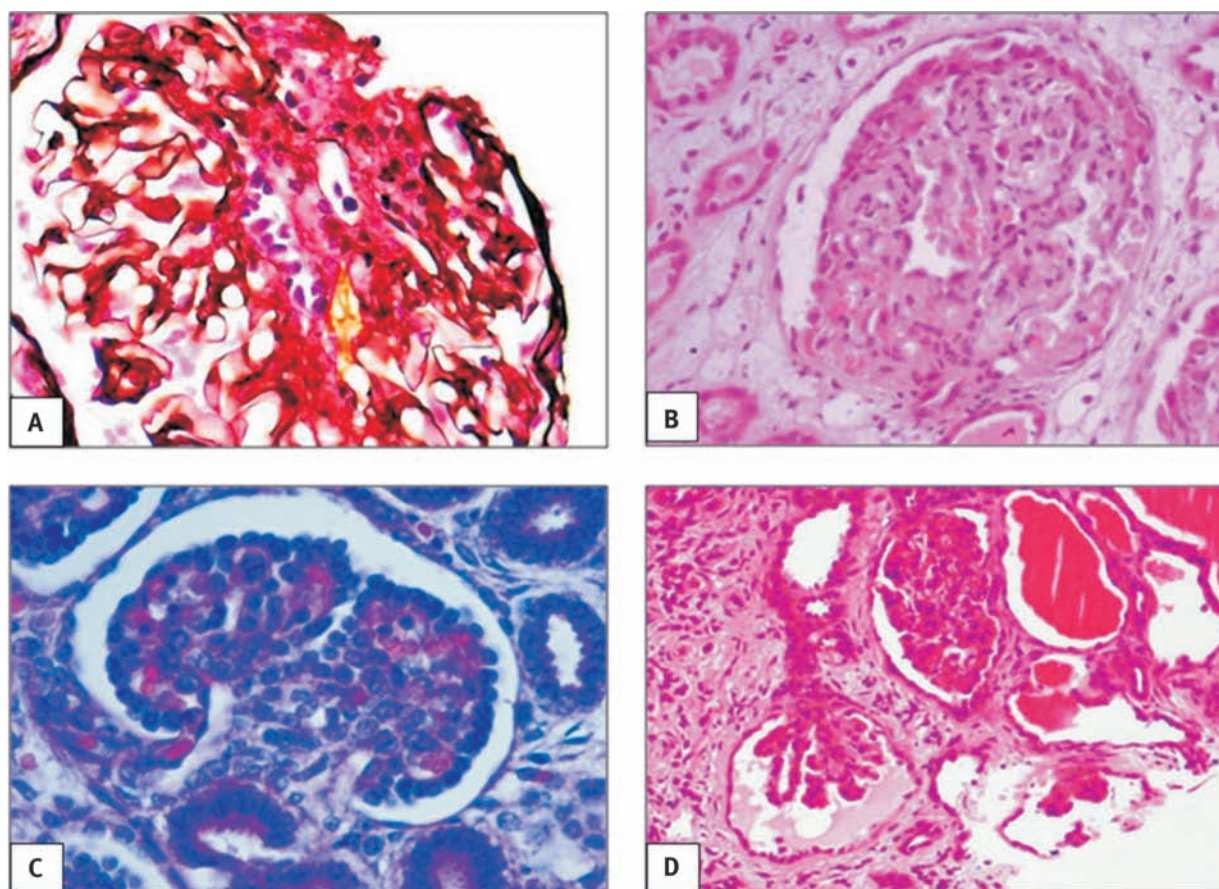


Figure 2

Panel A – D: Some histological variants of HIV-associated renal disease frequently seen in HIV-positive patients in Cape Town South Africa.

Panel A: Silver methenamine stain of a glomerulus showing features of “central sclerosis”; **Panel B:** Haematoxylin and eosin (H & E) stain of a glomerulus showing epithelial cell hypertrophy akin to that seen in normal fetal glomeruli shown in **Panel C** for comparison; **Panel D** shows classic collapsing glomerulopathy of HIVAN with adjacent microcystic tubular dilatation.

6.6% in the year 2000 to 25.7% in the year 2009 (a total of 262 biopsies in HIV-positive patients)¹⁴. Although we do not know if this is a reflection of the pattern of HIV kidney disease seen in other parts of Africa, this observation has been useful in providing us with vital understanding of the burden of kidney disease in our population. It has also resulted in the development of an HIV kidney disease classification, which we anticipate will aid in the prediction of treatment-based outcomes.

Aside from the non-performance of renal biopsies, there is also the challenge of the 'high cost' and unavailability of simple diagnostic tests required in day-to-day clinical practice or the performance of valid clinical research³. A study in Kenya that identified a high prevalence of kidney disease in an untreated HIV-positive population was only able to use a single urine dipstick and one measurement of serum creatinine to assess renal disease¹⁵.

■ 3. Renal replacement therapy in HIV-positive patients

From the early 1990s until the late 2000s, HIV positivity in many African countries automatically excluded individuals from renal replacement therapy (RRT). Although there were several reasons for this, lack of understanding of the disease and lack of adequate human resources to handle the extent of the epidemic contributed significantly to many patients being refused RRT. Africa has the lowest number of physicians and nephrologists per million population compared to any other continent. The number of nephrologists per million population in Nigeria, Ghana, Kenya and South Africa is reported to be 0.6, 0.1, 0.5 and 1.1 respectively, while this number is estimated to be 5.3 in the UK^{16,17}. In addition to having few nephrologists to tackle the burden of HIV renal disease, Africa has lost several medical practitioners to Western countries through the so-called 'brain drain' syndrome¹⁸. Such factors will continue to hamper the ability of the continent to tackle the burden of renal disease in HIV at any level.

One of the gains from the roll-out of cART in Africa has been the acceptance of many patients into the RRT programme. Patients with stable CD4 count and suppressed HIV viral load are now being accepted for RRT and transplantation. Since it would ordinarily be

impossible in resource-limited settings to readily find kidney donors for HIV-positive patients, Muller *et al.* from our centre recently reported the case of four HIV-positive patients who were transplanted using donors with HIV-positive kidneys¹⁹. The employment of HIV-positive donors would increase the donor pool, providing organs that otherwise would be discarded to recipients who would otherwise die of ESRD¹⁹.

■ FUTURE DIRECTIONS

Africans need to step up and find practical solutions to their own problems rather than relying on outsiders for help. Approaches such as voluntary counselling and testing, school-based interventions, prevention of mother-to-child transmission, treating sexually transmitted diseases, provision of condoms, male circumcision and female empowerment (all of which have been shown to be both effective and cost saving in the reduction and/or prevention of the transmission of HIV) need to be carried on²⁰. Also, increased awareness through various media programmes needs to be continued as this will help reduce the incidence of new infections and reduce the rate of complications, including kidney disease.

Regulatory bodies (governmental and non-governmental) must make policies that include more HIV-positive patients to receive cART therapy. On world AIDS day in 2009, the South African government announced that patients with CD4 count ≤ 350 cells/mm³ will be allowed to receive cART therapy (only patients with CD4 count < 200 cells/mm³ were previously included)²¹. This is a step in the right direction and measures to include more patients will definitely reduce the burden of complications associated with HIV infection, including kidney diseases.

Furthermore, practical approaches such as the chronic disease prevention and control proposed by WHO and the Kidney Disease Improving Global Outcomes (KDIGO) approaches and initiatives towards the public health problems of CKD are often appropriate for resource-limited countries^{22,23}. Specifically, all countries should have a targeted screening programme for CKD, tests for CKD should be performed frequently and include both urine test for proteinuria and a blood test for creatinine to estimate

GFR²³. The application of such approaches to patients with HIV will ensure routine monitoring before commencing and during treatment with cART. This approach will also ensure that patients with renal abnormalities are quickly identified for prompt referral and follow-up by a nephrologist.

Research on kidney disease in Africa should now focus on prospective clinical trials of immunosuppression in patients with HIV-immune complex kidney disease, biomarkers of kidney disease in HIV and prospective outcome studies in patients with HIV, treated with different regimes of cART. Classification of kidney disease in HIV will help to unify the histological terms used to describe kidney pathology seen in HIV patients and will help to identify risk factors for developing the different types of histological disease. This can be achieved through collaborative work with other researchers in this field.

Despite the slow progress, many patients in Africa with kidney disease from HIV infection are beginning to be identified and treated. The recent report of Muller *et al.*¹⁹ shows that significant strides can be made in the field of HIV-related kidney disease, and, as it turns out, a momentous leap might well come from Africa.

Conflict of interest. None declared.

References

- World Health Organization UNAIDS *Global summary of the AIDS epidemic, December 2007* [online], http://data.unaids.org/pub/GlobalReport/2008/2008_globalreport_core_en.ppt#268,3,Slide%203 (2008)
- Chigwedere P, Essex M. AIDS denialism and public health practice. *AIDS Behav.* 2010;14:237-47
- Arendse CG, Wearne N, Okpechi IG, Swanepoel CR. The acute, the chronic and the news of HIV-related renal disease in Africa. *Kidney Int* 2010;78:239-45
- Rao TK, Filippone EJ, Nicastri AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;310:669-73
- D'Agati V, Appel GB. HIV infection and the kidney. *J Am Soc Nephrol* 1997;8:138-152
- Klotman PE. HIV-associated nephropathy. *Kidney Int* 1999;56:1161-1176
- Szczzech LA, Gange SJ, Van Der Host C et al. Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int* 2002;61:195-202
- Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005;67:1381-1390
- Gerntholtz TE, Goetsch SJW, Katz I. HIV-related nephropathy: A South African perspective. *Kidney Int* 2006;69:1885-1891
- Arendse CR, Okpechi IG, Swanepoel CR. Acute dialysis in HIV positive patients in Cape Town South Africa. *Nephrology* 2010; Accepted Article; doi: 10.1111/j.1440-1797.2010.01358.x
- Peters PJ, Moore DM, Mermin J, et al. Antiretroviral therapy improves renal function among HIV-infected Ugandans. *Kidney Int* 2008;74:925-929
- Mulenga LB, Kruse G, Lakhani S, et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 2008;22:1821-1827
- Fuiano G, Mazza G, ComiN, et al. Current indications for renal biopsy: a questionnaire-based survey. *Am J Kidney Dis* 2000;35:448-457
- Okpechi I, Swanepoel C, Duffield M, et al. Patterns of renal disease in Cape Town South Africa: a 10-year review of a single-centre renal biopsy database. *Nephrol Dial Transplant* 2010 doi:10.1093/ndt/gfq655
- Wools-Kaloustian K, Gupta SK, Muloma E, et al. Renal disease in an antiretroviral-naïve HIV-infected outpatient population in Western Kenya. *Nephrol Dial Transplant* 2007;22:2208-12
- Katz IJ, Gerntholtz T, Naicker S. Africa and Nephrology: The Forgotten Continent. *Nephron Clin Pract* 2011;117:C320-C327 DOI:10.1159/000321524
- The UK Renal Registry. National Renal Review 2002: summary report on adult and paediatric renal services. http://www.renalreg.com/Documentation/renal_survey_2003_interim.pdf
- Eastwood JB, Conroy RE, Naicker S, et al. Loss of health professionals from sub-Saharan Africa: the pivotal role of the UK. *Lancet* 2005;365:1893-1900
- Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. *N Engl J Med* 2010;362:2336-7
- Galárraga O, Colchero MA, Wamai RG, Bertozzi SM. HIV prevention cost-effectiveness: a systematic review. *BMC Public Health* 2009;9(Suppl 1):S5 doi:10.1186/1471-2458-9-S1-S5
- Mail and Guardian online (2009) December 1st. <http://www.mg.co.za/%20article/2009-12-01-govt-steps-up-fight-against-aids>
- Epping-Jordan JE, Galea G, Tukuutonga C, Beaglehole R. Preventing chronic diseases: taking stepwise action. *Lancet* 2005;366:1667-1671
- Levey A, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007;72:247-259

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