HIV-Associated Renal and Genitourinary Comorbidities in Africa

Robert Kalyesubula, MBChB, MMed, FISN,*†‡ Nicola Wearne, MBChB, FCP, Cert Neph,§ Fred C. Semitala, MBChB, MMed, MPH,*‡¶ and Kasonde Bowa, FRCS¶

Abstract: With the recent massive scale-up of access to antiretroviral therapy (ART) in resource-limited countries, HIV has become a chronic disease with new challenges. There is mounting evidence of an increased burden of renal and genitourinary diseases among HIV-infected persons caused by direct HIV viral effects and/or indirectly through the development of opportunistic infections, ART medication-related toxicities, and other noncommunicable diseases (NCDs). We review the epidemiology of HIV-associated renal and urogenital diseases, including interactions with kidney-related NCDs such as hypertension, diabetes mellitus, and cardiovascular disease. We also examine the current evidence regarding the impact of HIV infection on the development of urogenital diseases. Highly advisable in sub-Saharan Africa are the establishment of renal disease registries, reviews of existing clinical practice including cost-effectiveness studies, and the adoption and use of HIV-related NCD management, with training for different cadres of health providers. Epidemiological research priorities include prospective studies to evaluate the true prevalence and spectrum of HIV-related renal disease and their progression. Simple diagnostics tools should be evaluated, including urinary dipsticks and point-of-care urea and creatinine tests to screen for kidney injury in primary care settings. Study of urological manifestations of HIV can help determine the extent of disease and outcomes. As patients live longer on ART, the burden of renal and genitouriological complications of HIV and of ART can be expected to increase with a commensurate urgency in both discovery and evidence-based improvements in clinical management.

Key Words: HIV/AIDS, noncommunicable diseases, kidney disease, urogenital disorders/disease, Africa, antiretroviral therapy

Methods

We found 2012 references (Box 1), of which we deemed 137 to be critical to our appraisal. We excluded studies that were focused solely on higher resource settings (except in cases where there were no data at all from SSA), not in English, case reports, and duplicates. For studies with similar methodology and/or information from same cohort or country, we selected the one with the highest patient numbers. The summary of our findings is presented in topical sections below.
HIV and CKD in SSA

CKD is defined as either evidence of structural or functional kidney damage (abnormal urinalysis, imaging studies, or histology) present for at least 3 months with or without a decreased glomerular filtration rate (GFR); OR, decreased kidney function (GFR < 60 mL·min⁻¹·1.73 m⁻²), with or without evidence of kidney damage.³⁶ CKD often presents without symptoms until it is in the advanced stage. CKD can be caused, accelerated, or complicated by HIV, with a low total CD4⁺ cell count < 200 cells per cubic millimeter identified as a strong predictor of kidney injury in at least 1 study.²⁷ CKD is classified into 5 stages of progression based on the estimation of the GFR, which is most often based on Cockcroft–Gault estimates and not the newer more robust Chronic kidney disease-Epidemiology Collaboration (CKD-EPI) GFR estimates.¹³,³⁸

The first 3 stages are often asymptomatic, whereas stage 4 and stage 5 may be symptomatic. It is, therefore, important to screen for CKD by urine protein and/or GFR earlier in the disease continuum before potentially irreversible damage occurs.

With only rare renal registries, the prevalence of HIV-associated renal diseases in Africa has not been precisely determined and prevalence rates reported by different studies vary. In Burundi, a CKD prevalence of 45.7% was reported in HIV-infected individuals.²⁴ In a large cohort of 25,779 ART-naive individuals conducted in Zambia among patients with renal insufficiency, 73.5% had stage 2 CKD (60–89 mL/min), 23.4% had stage 3 (30–59 mL/min), and 3.1% had stage 4 or 5 CKD (< 30 mL/min).²⁶ By comparison, HIV was associated with reduced renal function and progression to AIDS in an ART-naive cohort of 7383 patients with a mean CD4⁺ cell count of 385/mm³ in Western Kenya.²⁶,³⁸ The differences in prevalence may reflect differing methods of ascertainment. Well-designed studies are needed to determine the true prevalence, risk factors, and effective interventions for HIV-related kidney disease in SSA.

Direct Effects of HIV on the Kidney: HIV-Associated Nephropathy and Other Nephropathies

HIV-associated nephropathy (HIVAN) is a distinct histopathologic entity characterized by a collapsing focal glomerulosclerosis with microcystic tubular dilatation on histological examination.⁴⁰ HIVAN is common in HIV-infected people and typically presents with significant proteinuria, in patients with very low CD4 cell counts (< 200 and often < 100). Histological features of HIV-associated nephropathy among South Africans have been described.⁴¹–⁴³ In the largest renal biopsy series described to date, HIVAN was identified in 54% of 192 patients, making it the most common renal pathology.²² HIVAN, if untreated, is rapidly progressive to end-stage renal disease and death. Data from South Africa demonstrated 50% mortality at...
Given the very high mortality associated with HIV, diagnosis is critical. HIVAN is more common among black persons of African origin. Several studies have shown that variation in MYH9 (nonmuscle myosin IIa heavy chain) and APOL1 genes on chromosome 22 predispose to focal segmental glomerulosclerosis (FSGS), HIVAN, and hypertensive ESRD. Noncoding genetic variants in the MYH9 gene are associated with the development of HIVAN, with ORs of up to 8 and an attributable risk fraction of 100%. These variants are common (>60%) in African descent individuals, but rare or absent in non-Africans. Two independent coding alleles in the APOL1 gene are in strong linkage disequilibrium with MYH9 risk alleles, confer resistance to Trypanosoma brucei rhodesiense infection (etiologic agent for African sleeping sickness), and are even more strongly associated with HIVAN, FSGS, and hypertension-attributed ESRD in African Americans, with ORs of 29, 10.5, and 7.3, respectively. Most African American patients with HIVAN have 2 APOL1 risk alleles, but other as yet unknown factors (possibly genetic, environmental, or viral) may influence the development of this disorder in some who have no or just 1 APOL1 risk allele.

Few data describe the prevalence of these chromosome 22 risk variants among HIV-infected populations in SSA. While researchers from Nigeria found a high frequency of 2 APOL1 risk alleles in the general population of Igbo people of south-eastern Nigeria (23%) and noted a nearly 3-fold higher (67%) allele frequency in the CKD population, studies from Ethiopia have shown that the risk variants are uncommon. Little is known about the correlation of these genetic variants to sleeping sickness prevalence. More SSA studies can assess regional variations of these risk alleles/genetic variants.

Impact of Other NCDs on the Kidney: Hypertension, DM, and CVD

While hypertension and renal disease were found to be more common in HIV-infected individuals from high-income countries with a prevalence of 13%–34%; in a cohort study of 5563 HIV-infected patients in Uganda, hypertension was found in 28% of all study participants and in 49% of those >50 years of age. For the 786 patients receiving renal function testing, 9 (1.2%) had abnormal creatinine concentrations. These figures are likely to increase as the population ages because kidney disease prevalence increases with age.

Studies conducted in the United States show that, overall, hypertension was more common in blacks (32%) than in whites (23%) and African Americans are more likely to be hospitalized for cardiovascular-relation disease than their white counterparts. In a survey of close to 1.5 million hospital discharges (1996–2008), the odds of cardiovascular-related hospitalizations in HIV-infected patients were 45% higher for African Americans than whites (OR = 1.45; 95% CI: 1.39 to 1.51) after controlling for potential confounders. Kidney disease was independently associated with increased odds of hospitalization (OR = 1.43; 95% CI: 1.36 to 1.51). Despite antihypertensive therapy, African Americans have been demonstrated to have a higher incidence of advanced renal disease in the African American study of kidney disease and hypertension, suggesting that genetics, lifestyle, and/or access to screening and treatment might be primarily responsible. The genetic hypothesis is supported by the fact that kidney disease in African American study of kidney disease and hypertension participants was strongly associated with the APOL1 renal variants. The genetic overlap between hypertension, FSGS, and HIVAN may explain the development of hypertension and CKD in those HIV-infected patients living longer on ART.

The interaction between DM and kidney disease has been well documented in the African context, with DM identified as one of the leading causes of both AKI and CKD. However, the link between HIV, CKD, and DM is not well characterized by more than a handful of studies from Africa. In a study of 300 HIV-infected patients in a primary health care setting in Congo, a familial history of DM was significantly associated with kidney disease (adjusted OR = 2.20; 95% CI: 1.07 to 4.5). DM was one of the major factors for CKD among HIV-infected patients in South Africa. A national US cohort of HIV-infected and matched HIV-uninfected military veterans demonstrated a rate of progression to CKD of 4% with neither HIV nor DM, compared with 18% for persons with both. Hence, patients with both HIV and DM were at increased risk of progressive CKD even after adjusting for traditional CKD risk factors. Similar studies in SSA should evaluate contribution of differences in health care access, genetics, and available interventions.

CVD is on the rise in SSA and are associated with increased mortality. In the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) study carried out from 12 SSA hospitals in 9 countries, 1006 patients with a previous acute heart failure event were enrolled in prospective registry. HIV infection and kidney dysfunction were among the major predictors of 180-day mortality. The interaction between HIV, kidney disease, and other NCDs is complex and poses many unanswered questions in SSA (Figure 1).

Impact of Drugs Used in HIV on the Kidneys

Drug toxicities to the kidneys are common in the setting of HIV and may be because of ART or the drugs used to treat opportunistic infections. The main culprits are tenofovir, disoproxil fumarate (TDF), rifampicin, co-trimoxazole, and amphotericin B, which are commonly used in SSA. TDF-based ART has now become the preferred first-line regimen in most of SSA. Although data are still scarce in SSA, studies have noted an increased risk of kidney injury from TDF-based regimens, especially if combined with protease inhibitors. TDF classically induces nephrotoxicity to proximal tubular cells that may be associated with a Fanconi-like syndrome. A simple dipstick showing glycosuria in a normal glycemic individual would be highly suggestive of this condition. On TDF withdrawal, renal function normally improves; however, there are case reports of continued
progression to CKD. In a meta-analysis of 17 studies examining TDF safety, a significantly greater loss of kidney function among the TDF recipients was observed, compared with control subjects, as were greater acute kidney injuries.

With the exception of the newer agents (tipranavir and darunavir), protease inhibitors have been associated with urinary stones (nephrolithiasis) and crystal nephropathy. The commonly implicated drugs are indinavir, amprenavir, and atazanavir. Some of these drugs often need refrigeration and are not readily available in SSA; they are not a significant cause of kidney injury in SSA. The commonly used protease inhibitor lopinavir/ritonavir is usually reserved for second-line therapy.

Other antiretroviral agents, including entry inhibitors (enfuvirtide), CCR5 antagonists (maraviroc and vicriviroc), and integrase inhibitors (raltegravir and elvitegravir), are rarely used in SSA. These drugs are relatively safe to the kidney. It is critical that drugs causing nephrotoxicity are avoided, where possible, in circumstances of renal impairment, and if necessary for treatment, are dose-adjusted appropriately.

**Diagnosis and Management of Kidney Disease in SSA**

The monitoring of kidney disease in resource-limited regions are ongoing challenges in most African settings. The CKD-EPI equation has been reported to be more accurate in a Kenyan cohort where all formulas were compared with a direct GFR measurement by iothalamate clearance using a filter paper-based assay. The challenge here is that these are computer-based formulae that may not be readily applicable in remote areas of Africa. Fortunately, both the Cockcroft-Gault and Modification of Diet in Renal Disease formulae have been validated in an African setting by the DART trial and the Cockcroft-Gault can be determined using a simple calculator. Laboratories should be encouraged to include an estimated GFR for every creatinine report.

Routine renal work-ups should include creatinine and urine dipsticks, with further investigation if these are abnormal. Urine dipstick screening is inexpensive, benign, and acceptable to patients; cost-effectiveness is likely higher in at-risk patients compared with the general population. Renal ultrasound is important, but is not always available and may be nonspecific for renal diseases that do not cause anatomical distortions. Other diagnostics should be examined for their utility, including oral urease and creatinine point-of-care tests.

These tests may be easier to perform, but their specificity, sensitivity, and cost-effectiveness must be studied in resource-limited settings. The use of novel urinary biomarkers such as NGAL (neutrophil gelatinase-associated lipocalin) and KIM-1 (kidney injury molecule-1) are potential screening tests as well as mortality predictors in resource-poor settings, but their use will highly depend on the cost and clear guidelines for their clinical use.

Use of technology such as mobile and electronic health could potentially link patients from resource-limited settings.
### TABLE 1. Key Studies for HIV and Renal and Genitourinary Comorbidities in Africa

<table>
<thead>
<tr>
<th>Disease</th>
<th>References</th>
<th>Country</th>
<th>Sample</th>
<th>Study Type</th>
<th>Brief Study Description</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI/CKD</td>
<td>Vachiat et al[^{21}]</td>
<td>SA</td>
<td>684 with kidney failure</td>
<td>R,O (101 HIV+)</td>
<td>Survey for AKI and CKD and outcomes for HIV-infected and noninfected patients in SA tertiary hospital between 2005 and 2006</td>
<td>57 (56%) HIV-infected had AKI with sepsis as the leading cause. Mortality rates were similar in the HIV-infected and noninfected group</td>
</tr>
<tr>
<td>CKD</td>
<td>Cailhol et al[^{24}]</td>
<td>Burundi</td>
<td>300 (215 on ART)</td>
<td>CS</td>
<td>Multicenter study examined prevalence and nature of CKD among HIV-infected patients using GFR with proteinuria</td>
<td>Prevalence of CKD found at 45.7% with use of nonsteroidal anti-inflammatory drugs, high viral load and tuberculosis as key associations for CKD in HIV</td>
</tr>
<tr>
<td>CKD</td>
<td>Mulenga et al[^{26}]</td>
<td>Zambia</td>
<td>25,779</td>
<td>P,O</td>
<td>ART-naive cohort study to examine the association between baseline renal disease and mortality among adults initiating ART</td>
<td>33.5% had CKD. The risk of 90-day mortality increased with the stage of CKD among the HIV-infected patients</td>
</tr>
<tr>
<td>HIVAN</td>
<td>Wearne et al[^{12}]</td>
<td>SA</td>
<td>221 (192 renal biopsies)</td>
<td>P,O</td>
<td>Renal biopsies from HIV-infected patients were analyzed to determine outcomes and prognostic indicators based on histology and clinical features</td>
<td>HIVAN most common histology (54%) and immune complex disease found in 30% of patients. ART reduced mortality by 57%. HIVAN occurs at high CD4 counts</td>
</tr>
<tr>
<td>HIVAN</td>
<td>Han et al[^{41}]</td>
<td>SA</td>
<td>615 (32 renal biopsies)</td>
<td>CS</td>
<td>HIV-infected ART-naive patients were screened for proteinuria and renal biopsies done as needed in a single center study</td>
<td>HIVAN most common finding (85%) but the study excluded patients with HTN, DM, ESRD, and those with known causes of CKD</td>
</tr>
<tr>
<td>HIVAN</td>
<td>Gerntholtz et al[^{43}]</td>
<td>SA</td>
<td>90 renal biopsies HIV-infected patients</td>
<td>R,O</td>
<td>Renal biopsies done in HIV-infected black African patients to determine the prevalence of both “classic HIVAN” and non-HIVAN pathologies compared to HIV-negative patients</td>
<td>“Classic HIVAN” noted in 27% and “HIVICK” in 21%, those without HIV had none of these 2 entities but presented with minimal change and membranoproliferative disease</td>
</tr>
<tr>
<td>Non-diabetic CKD</td>
<td>Ulasil et al[^{18}]</td>
<td>Nigeria</td>
<td>87 (44 CKD; 43 controls)</td>
<td>Case control</td>
<td>Nondiabetic CKD and controls used to quantify the association of APOL1 risk alleles with CKD in the general population of Igbo people of southeastern Nigeria</td>
<td>Two APOL1 risk alleles prevalent in 23.3% in general population but 66% in the CKD patients. APOL1 may explain the increased prevalence of CKD in this region especially in the HIV-infected patients</td>
</tr>
<tr>
<td>HTN, CVD</td>
<td>Mateen et al[^{10}]</td>
<td>Uganda</td>
<td>5563 (786 patients with P,O RFTs)</td>
<td>P,O</td>
<td>Ambulatory clinic-based study of hypertension and projected 10-yr absolute risk of acute CVD HIV-infected youth and adults</td>
<td>The prevalence of HTN found in 28% of all participants, while 9 of 786 (1.2%) had abnormal creatinine levels. Of 1102 patients with complete results, 20% of men were at least 10% or more long-term risk of acute CVD</td>
</tr>
<tr>
<td>DM, HTN</td>
<td>Longo et al[^{17}]</td>
<td>Congo</td>
<td>300 (88% on ART)</td>
<td>CS</td>
<td>Adult study to evaluate the prevalence of low GFR, proteinuria, and associated risk factors among HIV-infected patients in primary health care</td>
<td>Familial history of DM and HTN were significantly associated with proteinuria. Severe immunodeficiency was a risk factor for CKD</td>
</tr>
<tr>
<td>CVD, HF</td>
<td>Sliwa et al[^{39}]</td>
<td>Multiple (9 SSA countries)</td>
<td>9906 (500 HIV tested)</td>
<td>P,O; multicenter</td>
<td>A clinical registry for patients with acute heart failure used to study factors prognostic of readmission and death in 12 SSA hospitals</td>
<td>HIV infection and kidney dysfunction were among the major predictors of 180-day mortality</td>
</tr>
<tr>
<td>TDF renal toxicity</td>
<td>De Beaudrap et al[^{11}]</td>
<td>Senegal</td>
<td>428 (40 patients on TDF regimens)</td>
<td>P,O</td>
<td>HIV-infected patients with and without TDF were followed up for 42 wks to determine effect on GFR</td>
<td>A significant decline in renal function was observed in one-third of the patients receiving TDF compared with patients not receiving TDF</td>
</tr>
</tbody>
</table>
We believe persons living with HIV/AIDS should be included in chronic dialysis programs. This method has worked well for other diseases like DM and hypertension, as well as general HIV/AIDS care. This is largely been underutilized in most resource-limited settings; however, new optical technologies may make cameras more relevant in pathological diagnosis.

TABLE 1. (Continued) Key Studies for HIV and Renal and Genitourinary Comorbidities in Africa

<table>
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<th>Study Type</th>
<th>Brief Study Description</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urological cancer, infertility, ED</td>
<td>Heyns et al109</td>
<td>Multiple</td>
<td>Not specified</td>
<td>Review</td>
<td>Authors reviewed the literature for common urological presentations in HIV-infected patients</td>
<td>Urological cancer occurs in 15% of HIV-infected patients and 30%–50% with AIDS; neurological diseases occur in 30%–40% with AIDS, KS, and NHL common</td>
</tr>
<tr>
<td>Urethral strictures</td>
<td>Labib, 2013110</td>
<td>Zambia</td>
<td>71 (26 HIV-infected)</td>
<td>P,O</td>
<td>Short-term outcomes of treatment of urethral stricture disease were compared between HIV-infected and noninfected patients</td>
<td>50% of patients with posturethritis strictures were HIV infected. HIV status influenced the site and length of the stricture but not the recurrence rate</td>
</tr>
<tr>
<td>Infertility</td>
<td>Bowa et al111</td>
<td>Zambia</td>
<td>34 (9 HIV infected)</td>
<td>P,O</td>
<td>All patients attending a fertility clinic were enrolled. HIV status and 3 semen samples were analyzed</td>
<td>HIV infection was significantly higher (26%) in men seeking fertility treatment than in the general population (13%)</td>
</tr>
<tr>
<td>FUS</td>
<td>Downs et al112</td>
<td></td>
<td>457 (26 HIV infected)</td>
<td>CS</td>
<td>Community-based study in women to determine prevalence of FUS</td>
<td>FUS more prevalent in HIV-infected patients compared with the general population</td>
</tr>
</tbody>
</table>

CS, cross-sectional study; ED, erectile dysfunction; FUS, female urogenital schistosomiasis; HIVCK, HIV immune complex kidney disease; HF, heart failure; HTN, hypertension; P,O, prospective, observational; R,O, retrospective, observational; SA, South Africa.

Renal biopsy, the gold standard to correctly document renal disease, is not widely available in Africa, where most countries lack nephrologists, histopathologists, or both. Pathology slides could potentially be shared through Internet with subsequent video conferencing discussions to guide diagnosis and management, with commensurate quality improvement and potentially saving both time and resources. New optical technologies may make cameras more relevant in pathological diagnosis.

National Kidney Foundation guidelines suggest screening individuals with hypertension, DM, CVD, renal tract structural disease, and those with family history of kidney disease. We believe persons living with HIV/AIDS should be part of this list of priority patients for screening, especially if they are of African descent. We recommend using dipsticks plus yearly serum creatinine testing. If the dipstick urine protein is positive, proteinuria needs to be quantified with a protein/creatinine ratio. Renal ultrasound should be performed if abnormalities are detected.

Management of CKD in SSA, especially ESRD, is expensive and care is too often based on the ability of the patient to pay. Hemodialysis costs have been estimated to be between US$7000 and $55,000 per patient per year, depending on whether the facility is private or government supported. Chronic dialysis programs are not publicly funded in most SSA countries. In South Africa, there is government funding, but only a limited number of patients are accepted/eligible. HIV-infected patients are eligible only if they have a CD4 count >200 cells per microliter, a suppressed viral load, and if space is available in the dialysis center. Given the current difficulties in accessing hemodialysis, other effective and more cost-efficient alternatives such as peritoneal dialysis need further exploration. Peritoneal dialysis has largely been underutilized in most resource-limited settings; yet, it is highly effective and easily scalable as demonstrated in Tanzania and other African countries.

Renal transplantation is now possible for HIV-infected patients in some centers in South Africa. In general, patient and graft survival rates fall between those reported in the national database for older kidney transplant recipients (≥65 years) and those reported for all kidney transplant recipients. There is also a higher rate of acute rejection episodes among HIV-infected transplant recipients. In Cape Town, a program is underway evaluating HIV-infected donors with HIV-infected recipients. This program has given hope to many HIV-infected patients with ESRD who were previously not deemed eligible for renal transplant.

With the collision of the epidemics of hypertension, DM, and an aging HIV-infected population living longer on ART, a substantial impact on the mortality and morbidity from CKD is inevitable. Preventive and early detection efforts are certainly the most efficient approaches for SSA, given limited resources. Incorporating screening for hypertension, DM, and renal function using low-cost dipsticks and other tools in HIV clinics has been proposed. Table 1 summarizes key studies on HIV, NCDs, and kidney disease as well as genitourological (GU) conditions discussed in the next section.

HIV and GU Conditions

When the CD4 count declines below 500 cells per microliter, the GU system becomes prone to NCDs. This is because of a progressive decline in immunocompetence, direct viral effect, and opportunistic infections of the GU organs. The key NCDs common in SSA are oncological diseases of the GU (30%–50%), neurological diseases (30%–
These are compounded by infections of the GU system that increase with CD4+ cell counts <200 per microliter. Infections can be etiologic factors in acquiring some NCD, but also augment GU organ damage and worsen NCD prognosis. For example, urethral stricture disease can be an outcome of gonorrhea or chlamydia; strictures can be especially severe and intractable in HIV patients, presenting a major challenge to urological practice in Africa.

**Malignancies of the GU System**

The most common malignancy is Kaposi sarcoma (KS), which is 7000 times more common in HIV-infected people than the general population. The KS lesions may affect any of the GU organs with less than 3% involving the penis. Non-Hodgkin lymphomas are 60 times more common in HIV patients than in the general population. Non-Hodgkin lymphomas affect the kidney in 6%–12% of HIV-infected patients. Germ cell tumors of the testis are 20–57 times more common in HIV patients than the general population. Changes have been reported in the pattern of urological malignancies in some African countries with the advent of HIV infection. There has been an increase in cancer of the penis associated with human papillomavirus infection and a modest increase in transitional cell carcinoma of the bladder among HIV-infected patients. While Schistosoma haematobium is a possible risk factor for HIV acquisition in women due to genital ulcerations, there are so far no good studies describing the relationship between HIV, schistosomiasis, and bladder cancer.

**Neurogenic Effects on the GU System**

HIV-infected patients are seen with micturition disorders such as incontinence, urinary retention, and dysuria. Some of the symptoms are compounded by underlying urinary tract infections and bladder stones that are also common in these patients. These symptoms become more common with progression of disease and decline in CD4+ cell counts. The common causes are direct nerve injury such as HIV neuropathy and demyelination disorders. Additionally, infections such as cerebral toxoplasmosis and cytomegalovirus polyradiculopathies compound the neurological disorders. In roughly 20% of cases, the first presentation may be with micturition disturbances. Urodynamic findings in these cases include detrusor-sphincter dyssynergia, hypoactive bladder, hyperreflexia, bladder outflow obstruction, and hyporeflexia. Such patients are frequently treated with lean intermittent self-catheterization, α-blockers, and bladder compliance drugs as appropriate.

**RESEARCH PRIORITIES**

There are few renal and GU registries in SSA. Hence, there is an urgent need to establish audits and shared registries to characterize the overall burden of renal and urological diseases in SSA, as well as the specific contributions of HIV to urogenital and renal morbidity and mortality. The registries will also help to establish occurrence and severity of side effects to ART.

The shortage of health workers in Africa, especially in the sub-Saharan region, is the most acute in the world. A World Health Organization survey revealed that while Africa accounts for more than 24% of the global disease burden, it has only 3% of the world’s health workers and spends less than 1% of total global resources dedicated to health. For chronic HIV care and for other NCDs, task shifting has been successfully implemented with use of the lower health cadres taking on the roles of doctors. This model can be used to screen for renal and urological comorbidities along with HIV care. The practicalities, skill-set training and the infrastructure for this role transition need to be developed and successful models need to be subjected to cost-effectiveness studies. These models can then be replicated in other areas including screening and caring for patients with kidney disease.

The high prevalence of HIV in Africa and particularly SSA presents a unique opportunity to study the impact of HIV on the incidence of NCDs. We need to use the infrastructure of capable clinics to perform prospective longitudinal studies. There is need to determine if HIV increases the risk of NCDs and in particular CKD. It is also unknown whether patients with CKD and HIV have poorer outcomes as compared with HIV-negative cohorts. The effect of chronic infection and inflammation on the incidence of and rate of progression of kidney disease among HIV-infected patients is another priority area of research.

Although we know that ART can stabilize renal disease in HIV-infected patients, some are patients who fail to respond or respond poorly. There is a need to develop pilot studies to evaluate therapies for the treatment of HIVAN including use of earlier ART, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and steroids. There are small nonrandomized clinical trials from around the world that support the use of corticosteroids. However, the question of whether the benefits outweigh the risks of opportunistic infections still needs to be answered, more so in areas like SSA where tuberculosis is very prevalent.

More prevalence studies of MYH9 and APOL1 genes in CKD and HIV are needed in SSA, which is home to both HIV and trypanosomiasis. Studies from West Africa and Ethiopia have evaluated the prevalence and risk factors for APOL1, but more needs to be done for other SSA countries because of the genetic diversity within these regions.

There is limited information on urological manifestations of HIV/AIDS. These manifestations need to be well documented beginning with case series and then larger follow-up studies. With high prevalence of malignancies like KS and lymphomas in SSA, one would expect an exponential increase in HIV urological conditions, but documentation of these is still lacking. Many patients in SSA are also now on second-line treatments involving protease inhibitors.

The International Society of Nephrology has developed a fellowship training program for nephrologists from developing countries and has recently shifted the training of Africans to International Society of Nephrology–certified renal units in Africa. This effort has the clear advantage of...
graduating nephrologists with acquired expertise in local kidney diseases with appropriate research skills, and the ability to conduct studies of local treatment options. However, there is no standardized curriculum or examinations for the fellows. It is important that nephrology fellows and other lower cadres are trained in clinical care and research in kidney diseases using a standardized curriculum. Others have examined training needs for cohort studies on NCDs in resource-limited settings and provided some insights. Research also needs to focus on the feasibility and cost-effectiveness of Internet-based programs and tele-medicine to evaluate whether these provide cheaper and effective avenues for knowledge transfer between resource-rich and resource-limited countries.

Although the prevalence of renal and urological related challenges varies from one resource-limited country to another, the challenges in management defining the future research agenda are similar. The dual burden of infectious diseases and NCDs in SSA, as well as lifestyle, cultural, and genetic differences mean that results from high-income countries cannot be applied indiscriminately to the African context. General population cohorts like the one in Semin Nephrol. 2011;16:201–208, and collaborative cohorts in South Africa, Global Alliance for Chronic Diseases, and others could provide a platform for future studies. See Table 2 for our summary of research priorities in SSA.

CONCLUSIONS

The HIV epidemic and its associated burden of kidney disease presents daunting clinical management challenges in SSA, especially for renal replacement, given limited resources. Prevention and early screening methods and the establishment and maintenance of select patient cohorts/registries should be the focus of future interventions for kidney disease in HIV. The genitourinary system in HIV patients is prone to NCDs, correlated in part with declining immunologic status. Opportunistic infections that are highly prevalent in SSA often serve to worsen these NCDs. The dual burden of infectious diseases and NCDs in SSA and the diversity in resources and practices present a unique opportunity for outcomes research and exploration of creative new avenues for combating kidney and urological diseases in this context.

REFERENCES


TABLE 2. Research Priorities and Recommendations for HIV Renal and Urological Comorbidities in Africa

1. Establish renal registries in Africa, specifically the contribution of HIV-related renal disease
2. Study the feasibility and cost-effectiveness of using the infrastructure of preexisting clinics and NCD research cohorts to perform prospective longitudinal studies involving HIV-infected patients with renal disease
3. Invest in genetic studies, including APOL1 and trypanosomiasis. Study the genetic milieu in regions of Africa to determine regional variations
4. Study the spectrum and outcomes of urological manifestations in HIV-positive patients in low-resource settings, especially SSA
5. Study the benefits and cost-effectiveness of using an integrated model for HIV-NCD management compared with specialist care for individual NCDs
6. Validate the nephrology curriculum for different health cadres among the different African training institutions
7. Evaluate the use of simple diagnostic tools, such as dipstick, to screen for kidney injury among HIV-infected patients in routine care in resource-poor settings

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