The changing epidemiology of HIV-related chronic kidney disease in the era of antiretroviral therapy

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The epidemiology of kidney disease in HIV-infected individuals has changed significantly since the introduction of combination antiretroviral therapy (cART) in the mid 1990s. HIV-associated nephropathy (HIVAN), an aggressive form of collapsing focal segmental glomerulosclerosis (FSGS) caused by direct HIV infection of the kidney in a genetically susceptible host, emerged early in the HIV epidemic as a leading cause of end-stage renal disease. With the widespread use of cART, HIVAN is increasingly rare in populations with access to care, and the spectrum of HIV-related chronic kidney disease now reflects the growing burden of comorbid disease in the aging HIV population. Nonetheless, available data suggest that both HIV infection and cART nephrotoxicity continue to contribute to the increased risk of chronic kidney disease in HIV-infected individuals in the United States and Europe. Despite the genetic susceptibility to HIVAN in individuals of West African descent, limited data are available to define the prevalence and spectrum of HIV-related kidney disease in sub-Saharan Africa, which is home to two-thirds of the world's HIV population. In this mini-review, we characterize the changing epidemiology of HIV-related chronic kidney disease in Western nations and in sub-Saharan Africa.

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More than 30 years after the first cases of AIDS were reported in New York and California, an estimated 34 million individuals are living with HIV/AIDS worldwide.[1] Within 3 years of those first case reports, a unique kidney disease now known as HIV-associated nephropathy (HIVAN) was recognized among African-Americans and Haitian immigrants in large urban centers in the United States.[2] Histologically, HIVAN was described as a collapsing variant of focal segmental glomerulosclerosis (FSGS) with accompanying tubulointerstitial injury (Figure 1). Clinically, HIVAN was characterized as an aggressive glomerulopathy, emerging as a leading cause of end-stage renal disease (ESRD) among African Americans by the early 1990s.[3] The pathogenesis of HIVAN involves the local expression of viral genes in the kidney of a genetically susceptible host, and is the focus of an accompanying mini-review.[4]

Following the widespread introduction of effective combination antiretroviral therapy (cART) in 1996, the natural history and epidemiology of HIV infection and HIVAN have evolved in tandem. AIDS-related deaths and ESRD attributed to HIVAN have both declined in populations with access to care, and the spectrum of HIV-related kidney disease has changed to include more comorbid kidney diseases,[5] as well as nephrotoxicity related to chronic cART use.[6,7] Tragically, the greatest burden of HIV infection and HIV-related kidney disease has converged on a region of the world with limited resources for chronic disease management. It is estimated that two-thirds of the world's HIV-infected individuals live in Africa, with more than 97% of new infections occurring in low- and middle-income countries.[1] Consistent with our current understanding of the genetic susceptibility to HIVAN and other forms of FSGS in individuals of West African descent, available data suggest wide variability in the prevalence of HIVAN and other HIV-related kidney disease in different regions of sub-Saharan Africa. In this mini-review, we characterize the changing epidemiology of HIV-related kidney disease in the aging HIV population in the US and Europe, and in the growing HIV population in sub-Saharan Africa.

PATHOGENESIS OF HIVAN AND OTHER HIV-RELATED KIDNEY DISEASES

A detailed discussion of HIVAN pathogenesis is the subject of an accompanying mini-review.[4] HIVAN occurs almost

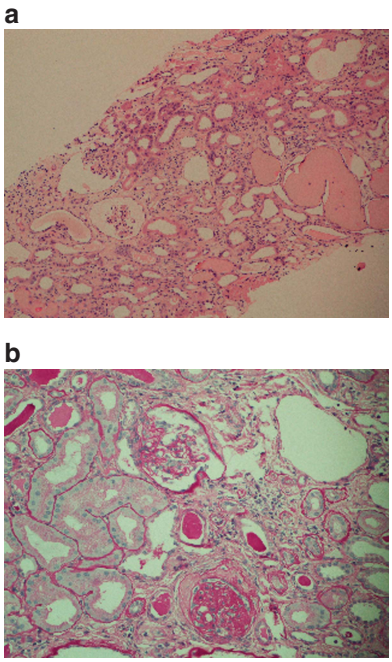

Figure 1 | Classic pathological features of HIV-associated nephropathy (HIVAN). Kidney biopsy performed in a 28-year-old African-American man with untreated HIV/AIDS presenting with heavy proteinuria (urine protein: creatinine ratio 7.8 g). At the time of presentation, serum creatinine was 5.9 mg/dl, CD4 cell count was 9 cells/mm^3, and plasma HIV-RNA was >900,000 copies/ml. (**a**) Low-power view demonstrating the typical pathologic features of HIVAN, including glomerular collapse, microcystic tubular dilatation with proteinaceous casts, and interstitial inflammation and fibrosis (hematoxylin and eosin (H&E), ×100). (**b**) High-power view of a glomerulus demonstrating the collapse of capillary loops, dilatation of the glomerular space, and hyperplasia of overlying podocytes (periodic acid–Schiff, ×400).

exclusively in the setting of advanced HIV disease, and studies in HIV-1 transgenic mice have established a direct role for local HIV infection of the kidney in genetically susceptible strains.[4] The central role of HIV infection is consistent with a plateau in the annual incidence of ESRD attributed to HIVAN following the introduction of cART in the US.[3] On the basis of these epidemiologic data and our current understanding of pathogenesis, a diagnosis of HIVAN is now considered a strong indication for the initiation of cART.[8] Nationally representative data from the US Renal Data System (USRDS) suggest that ~90% of the ESRD attributed to HIVAN occurs in African Americans.[3] Observational studies have also demonstrated a strong association between black race and the risk of chronic kidney disease (CKD) progression in HIV-infected individuals,[9,10] regardless of the etiology.[9] The increased susceptibility to HIVAN and other forms of CKD in HIV-infected African Americans is at least partly attributable to single-nucleotide polymorphisms in the apolipoprotein L1 (APOL1) gene, which are more common among individuals of West African descent.[11] The role of APOL1 in the kidney and the mechanisms of increased CKD risk associated with the polymorphisms are the subject of ongoing studies.

DEFINING HIV-RELATED KIDNEY DISEASE IN DIFFERENT POPULATIONS

The estimated prevalence of CKD among HIV-infected individuals varies substantially between studies, depending on region, study population, study design, and the definition of CKD used. The majority of studies have defined CKD as a creatinine-based estimate of glomerular filtration rate (GFR) below a certain threshold, most often <60 ml/min. Recent data comparing creatinine-based estimates with a direct measure of GFR suggest that the CKD Epidemiology Collaboration (CKD-EPI) GFR estimate has the highest accuracy in HIV-infected adults;[12–14] nonetheless, the majority of studies have been based on Cockcroft–Gault creatinine clearance or the Modification of Diet in Renal Disease (MDRD) GFR estimate. Although its independence from muscle mass has made serum cystatin C an appealing alternative to creatinine in HIV-infected individuals, available data suggest that cystatin C should not be used alone to estimate GFR in this population, and that the addition of cystatin C to creatinine provides only modest benefit.[12,13] Cystatin C–based GFR estimates do appear to be more predictive of nonrenal adverse outcomes in HIV-infected individuals, perhaps because serum cystatin C reflects both GFR and the systemic inflammatory milieu.[15,16]

In addition to the limitations and variability in GFR estimates used, a lack of consistent data on proteinuria has further hindered accurate estimates of CKD prevalence in HIV-infected individuals. Few studies have included protocol-driven measures of proteinuria, and the inclusion of clinically available measures of proteinuria or creatinine in some studies may have selected for a population at higher risk for CKD. Finally, few studies have included kidney biopsy, and those that have are inherently limited by referral bias. With these caveats, the evolving epidemiology of HIV-related kidney disease has been best characterized in the US and, to a lesser degree, in Europe and sub-Saharan Africa.

THE CHANGING EPIDEMIOLOGY OF HIV-RELATED KIDNEY DISEASE IN RESOURCE-RICH SETTINGS

Nationally representative data from the USRDS demonstrate a plateau in the annual incidence of ESRD attributed to HIVAN, with ~800–900 new cases reported each year in the US.[3] As the USRDS no longer collects data on comorbid HIV infection, the incidence of non-HIVAN ESRD in HIV-infected individuals is not well documented. In an urban cohort of African Americans with HIV infection, the annual incidence of ESRD was ~1%, with no significant difference following the introduction of cART.[17] Although these data are consistent with a rise in comorbid CKD offsetting a decline in HIVAN with cART, adherence to cART was not directly assessed and could have been insufficient to prevent HIVAN in this population with a high prevalence of current or prior injection drug use. Despite a plateau in incidence, these data demonstrate a rise in the prevalence of ESRD among HIV-infected individuals, largely as a result of improved survival in the cART era.

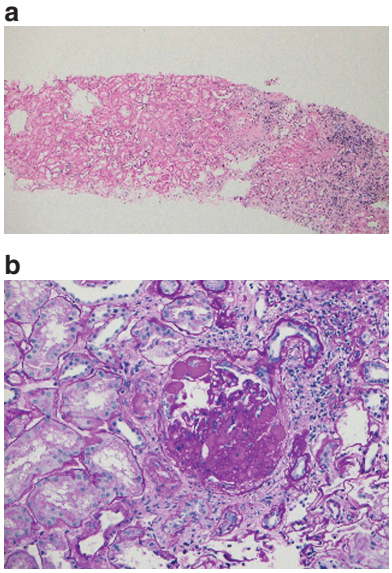

Figure 2 | Pathological features of noncollapsing focal segmental glomerulosclerosis (FSGS) in the setting of HIV infection. Kidney biopsy performed in a 30-year-old Hispanic black man with non-nephrotic proteinuria (~1.5 g) and well-controlled HIV infection on combination antiretroviral therapy (cART). At the time of presentation, serum creatinine was 1.5 mg/dl, CD4 cell count was >500 cells/mm^3, and plasma HIV-RNA was undetectable. Although the contribution of HIV infection to noncollapsing FSGS is not known, the increasing frequency of this diagnosis in cART-treated individuals is consistent with the hypothesis that these cases reflect partially treated HIV-associated nephropathy (HIVAN). (**a**) Low-power view demonstrating segmental glomerulosclerosis with surrounding interstitial inflammation and fibrosis. There is no evidence of glomerular collapse or microcystic tubular dilatation (hematoxylin and eosin (H&E), ×100). (**b**) High-power view of the glomerulus that shows segmental scarring, characterized by irregular accumulation of matrix, obliteration of capillary loops, and fibrous attachments to Bowman's capsule (periodic acid–Schiff, ×400).

Available data on the spectrum of histologic findings reinforce the importance of kidney biopsy for definitive diagnosis. In a series of 152 HIV-infected individuals undergoing clinically indicated kidney biopsy at a single center, the proportion with a histologic diagnosis of HIVAN decreased from 80% in 1997 to 20% in 2004.[5] This was accompanied by an increase in noncollapsing FSGS. Although noncollapsing FSGS in HIV-infected individuals has been hypothesized to represent partially treated HIVAN, it may also reflect the disproportionate burden of both HIV infection and genetic susceptibility to FSGS in individuals of West African descent (Figure 2). Retrospective biopsy series tend to reflect the spectrum of glomerular disease, based on the most common indications for kidney biopsy. In an autopsy series of patients with advanced HIV disease who were unselected for overt CKD, we identified a high prevalence of subclinical arteriosclerosis and interstitial inflammation.[18] Taken together, these data suggest that CKD in an individual chronically infected with HIV is now more likely to be a result of non-HIVAN kidney disease (Table 1). As patients live longer with cART, the burden of comorbid CKD and medication toxicity is likely to continue to grow. The direct contribution of HIV infection to non-HIVAN kidney disease is not known; however, available data suggest that HIV may have an independent effect on CKD progression, as discussed in the next section.

COMORBID CKD IN HIV: DIABETES, HYPERTENSION, AND HEPATITIS C CO-INFECTION

Diabetes and hypertension account for more than 70% of all ESRD in the general US population.[3] With aging of the HIV-infected population and prolonged exposure to cART regimens that may promote the development of diabetes and hypertension, the prevalence of comorbid CKD risk factors is increasing. Two longitudinal studies have suggested an additive effect of HIV infection and diabetes in promoting CKD progression in the US veteran population.[10,19] Diabetes and hypertension have also been identified as independent risk factors for CKD among HIV-infected individuals in Europe.[6] Recent murine studies indicate that an upregulation of local inflammation induced by HIV may aggravate diabetic nephropathy.[20] Further studies are needed to examine the mechanisms by which HIV infection may accelerate the progression of non-HIVAN CKD.

An estimated 10 million individuals worldwide are co-infected with HIV and HCV.[21] In a meta-analysis of randomized controlled trials and observational studies, HIV-HCV co-infection was also associated with a significant increase in the risk of CKD or CKD progression among HIV-infected individuals.[22] Although meta-analyses are limited by the quality of the individual studies, subsequent observational studies have supported the observed association between HIV-HCV co-infection and increased CKD risk. For example, HIV-HCV co-infection was associated with an increased risk of CKD in the Women's Interagency HIV Study[23] and in the Veterans' Aging Cohort Study.[24] In a combined analysis of data from two large international HIV treatment trials, both HCV seropositivity and higher HCV viral load were associated with an increased risk of CKD progression in cART-treated participants.[25] A similar association between HCV viremia and CKD risk was observed in EuroSIDA, a large European cohort study.[26] Although a recent analysis of data from NA ACCORD, a consortium of North American HIV cohorts, failed to detect a significant association between HCV viral load and CKD progression, this study did confirm the strong association with HCV seropositivity.[27] None of these studies could fully account for the type, frequency, and duration of injection drug use, an important potential confounder.[28] Although individuals with HIV-HCV co-infection may present with immune complex–related glomerulonephritis, most commonly membranoproliferative glomerulonephritis,[29] it is not clear whether this seemingly rare phenomenon explains the increased risk of CKD and CKD progression observed with HIV-HCV co-infection. Clinically indicated kidney biopsies in 29 adults with HIV-HCV co-infection demonstrated a decline in immune complex disease and an increase in noncollapsing FSGS in

Table 1 | Spectrum of HIV-related kidney disease

Established or hypothesized role of HIV infection or its treatment
HIV-associated nephropathy (HIVAN)
Antiretroviral nephrotoxicity
Tenofovir (proximal tubulopathy)
Indinavir (interstitial nephritis and crystal deposition)
Other protease inhibitors?
HIV-immune complex kidney disease
IgA nephropathy
Hypothesized additive effect of HIV infection or its treatment
Diabetic nephropathy
Unclear role of HIV infection or its treatment
Noncollapsing focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis, with or without hepatitis C virus
Membranous nephropathy, with or without hepatitis B virus
Arterionephrosclerosis

the cART era,[30] similar to findings in a larger biopsy series including patients with and without HCV co-infection.[5]

THE CONTRIBUTION OF CART NEPHROTOXICITY TO CKD IN HIV-INFECTED INDIVIDUALS

In addition to a hypothesized role for HIV infection in the progression of comorbid CKD, several studies have also linked specific cART agents to the increased risk of CKD or CKD progression.[6,7,31] In a large European cohort study, CKD (defined as a confirmed creatinine clearance $\leqslant 60$ ml/min per 1.73 m^2 or a 25% decline from a baseline <60 ml/min per 1.73 m^2) was associated with increasing cumulative exposure to the older protease inhibitor indinavir and the commonly used nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF), both of which have established nephrotoxic potential. A significantly increased incidence of decreased creatinine clearance was also observed with longer exposure to atazanavir, a commonly used protease inhibitor that has been implicated in nephrolithiasis similar to that observed with indinavir, although less frequently.[6] A subsequent analysis among US military veterans also demonstrated a strong association between CKD (defined as GFR <60 ml/min per 1.73 m^2) and cumulative exposure to TDF, with similar findings for indinavir. Increasing exposure to TDF was also associated with rapid GFR decline (defined as $\geqslant 3$ ml/min per 1.73 m^2 per year over 2 years) and proteinuria, whereas cumulative exposure to atazanavir was associated with rapid eGFR decline but not with CKD or proteinuria.[7] Most recently, analysis of data from another large European cohort demonstrated an association between confirmed eGFR <70 ml/min per 1.73 m^2 and cumulative exposure to TDF, atazanavir, or boosted lopinavir; this level of eGFR was also a strong predictor of TDF discontinuation. Only boosted lopinavir use was associated with eGFR <60 ml/min per 1.73 m^2 in this study, although the authors speculate that the frequent discontinuation of TDF may have prevented further GFR decline.[32] This hypothesis is supported by the stabilization or improvement in GFR observed in a small study of 24 men who discontinued TDF with a GFR <60 ml/min per 1.73 m^2; of note, recovery to baseline GFR occurred in less than half of these men after a median of 5 months.[33] The association of tenofovir with GFR decline is consistent with a pooled analysis of data from earlier longitudinal studies, which demonstrated a small but significantly greater mean decline in creatinine clearance with tenofovir-containing cART as compared with alternative cART regimens.[31] Although the clinical relevance of these epidemiologic associations is not clear, biologic plausibility is supported by the known potential for tenofovir and the protease inhibitors to cause acute kidney injury. The potential for TDF and/or certain protease inhibitors to promote CKD progression warrants further study given the widespread use of these agents. Any observed increase in CKD risk must be weighed against the known benefits of cART.

THE SPECTRUM OF HIV-RELATED KIDNEY DISEASE IN SUB-SAHARAN AFRICA

More than two-thirds of the world's HIV-infected individuals live in sub-Saharan Africa.[1] Despite the high prevalence of HIV infection and the known genetic susceptibility to kidney disease associated with West African descent, it has been more difficult to characterize the burden of CKD and the spectrum of HIV-related kidney disease in Africa. Available data have provided widely varying estimates of CKD prevalence among cART-naïve adults in different regions of Africa (Table 2), with the highest prevalence reported in Nigeria, the most populous nation in West Africa.[34–41] These differences reflect remarkable genetic heterogeneity across Africa, as well as substantial variability in access to care, local standards for the initiation of cART, and competing risk of AIDS-related mortality. In addition, the choice of GFR estimate may have a significant impact on the estimated prevalence of decreased GFR, as demonstrated by studies that have reported CKD prevalence based on more than one GFR estimate (Table 2). No large studies have used the CKD-EPI equation without adjustment for race, as suggested by published studies comparing GFR estimates with a gold-standard measure of GFR in sub-Saharan African populations.[14,42] Because few studies have assessed for proteinuria, the majority of studies have estimated the prevalence of CKD based on decreased GFR.

The highest prevalence of CKD among HIV-infected adults has been reported in Nigeria. In a cross-sectional study of 400 consecutive cART-naïve Nigerian adults without comorbid CKD risk factors, 36% of participants had dipstick proteinuria and nearly a quarter had a Cockcroft–Gault creatinine clearance <60 ml/min.[35] Although available data suggest that the Cockcroft–Gault equation may underestimate GFR in sub-Saharan African populations,[14,42] the high prevalence of CKD observed in this study is consistent with a high frequency of *APOL1* risk alleles in West African populations.[43] The majority of studies from Central, East, and Southern Africa have reported a lower prevalence of decreased creatinine clearance, although there is significant variability between

Table 2 | HIV infection and chronic kidney disease among cART-naive adults in sub-Saharan Africa

Reference	Site	N	Study design	CD4+ cell count, cells/mm^3	Comorbid risk factors excluded	Creatinine measured by protocol	Prevalence of proteinuria	Prevalence of eGFR <60 ml/min
Wools-Kaloustian *et al.*[34]	Kenya	389	Prospective cross-sectional	Mean 391	Yes	Yes	6.2%	11.5% (CG)
Emem *et al.*[35]	Nigeria	400	Prospective cross-sectional	Mean 247	Yes	Yes	36%	23% (CG)
Mulenga *et al.*[36]	Zambia	25,249	Clinical care cohort	17%<50	No	No Available in 71%	—	8.9% (CG), 3.2% (MDRD)
Reid *et al.*[41]	Kenya/Uganda	3316	Secondary analysis of randomized trial[a,b]	Median 86	No	Yes	—	7.2% (CG)
Peters *et al.*[40]	Uganda	508	Secondary analysis of randomized trial[a,c]	Median 122	No	Yes	—	42% (CG), 12% (MDRD)
Lucas *et al.*[37]	Uganda	1202	Prospective cohort	—	No	Yes Using banked sera	—	0.7% (MDRD)
Wyatt *et al.*[38]	Rwanda	677	Prospective cohort (women only)	Median 256	No	Yes	9%	25% (CG), 2.7% (MDRD), 2.4% (CKD-EPI)
Jao *et al.*[39]	Multiple	2495	HIV treatment program[a]	Median 295	No	No Available in 54%	—	eGFR < 50 ml/min 3.4% (CG), 2.5% (MDRD), 2.5% (CKD-EPI)
Han *et al.*[44]	South Africa	615[d]	Prospective cross-sectional[d]	Mean 251	Yes	Not applicable	6%	—
Fabian *et al.*[45]	South Africa	578	Prospective cross-sectional	Mean 130	No	Not applicable	8.8%	—

Abbreviations: CG, Cockcroft-Gault creatinine clearance; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
Participants in all studies were HIV-infected adults naive to combination antiretroviral therapy (cART). In some cases, participants had received mono or dual therapy, including single-dose nevirapine in women. Some studies excluded participants with comorbid risk factors for CKD, including diabetes, hypertension, sickle cell disease, or systemic lupus.
[a]Only participants eligible for cART were included in this analysis.
[b]Serum creatinine >4.1 mg/dl was an exclusion criteria for the randomized trial. Data on exclusion for creatinine were not provided in the primary publication.
[c]Creatinine clearance <25 ml/min was an exclusion criteria for the randomized trial. 7/1171 (0.6%) of those screened were excluded for creatinine clearance.
[d]Serum creatinine >2.8 mg/dl was an exclusion criteria.

different patient populations (Table 2). In studies that have also reported MDRD eGFR, the estimated prevalence of eGFR <60 ml/min per 1.73 m^2 has ranged from as high as 12% to <1%. Few studies have assessed proteinuria, but estimates from Kenya, Rwanda, and South Africa have reported a prevalence of 5–9% among HIV-infected, cART-naïve adults (Table 2).[34–41]

In contrast to the emerging data on comorbid CKD in HIV-infected populations in the US and Europe, little is known about the impact of comorbid disease on the epidemiology of HIV-related CKD in Africa. Prospective studies designed to evaluate the prevalence of HIV-related kidney disease have excluded participants with traditional CKD risk factors, and the prevalence of diabetes and hypertension has been low in nearly all studies where these data were reported. With expanding access to cART and Westernization of the diet in many African nations, it is likely that diabetes and hypertension will have an increasingly important role in the future.

Few studies have provided insight into the spectrum of kidney disease in HIV-infected African individuals, with the majority of studies conducted in South Africa. Two cross-sectional studies in cART-naïve South African adults demonstrated a similar 5–6% prevalence of persistent proteinuria or microalbuminuria, but with large discrepancies in the spectrum of kidney pathology. In Durban, HIVAN was the most common diagnosis (25/30 biopsies).[44] In contrast, the same investigators observed only one case of classic HIVAN in Johannesburg, where HIV immune-complex kidney disease was the predominant diagnosis (8/20).[45] In both studies, kidney biopsy was often performed in participants with low-grade proteinuria who may not have undergone kidney biopsy as part of routine clinical care. Studies including clinically indicated biopsies in patients both on and off cART have also reported HIVAN and HIV immune-complex kidney disease to be the most common diagnoses in HIV-infected South African adults.[46,47] The mechanism by which HIV may contribute to immune complex kidney disease has not been well described, although there are well-characterized cases of IgA nephropathy and other forms of immune complex disease associated with circulating immune complexes containing anti-HIV antibodies.[48] Further translational studies are needed to characterize this disease process, and the risk factors associated with incidence and progression of HIV immune-complex kidney disease should be evaluated in longitudinal studies.

The broad spectrum of HIV-related kidney disease in the same region of Africa suggests that genetic variability among South Africans from different ethnic groups may contribute to disease pathogenesis. In Nigeria, where CKD was observed in 38% of cART-naïve adults and the prevalence of *APOL1* risk alleles is presumed to be high, HIVAN was the most common diagnosis among participants undergoing kidney biopsy, and no cases of HIV immune-complex kidney disease were observed.[35] In contrast, no cases of HIVAN were identified in a cohort of 338 Ethiopian immigrants in Israel, among whom only two individuals were found to have a single copy of the *APOL1* risk alleles.[49]

With expanding access to cART across Africa, the epidemiology and spectrum of HIV-related kidney disease

are likely to change. The majority of available studies have described the burden of CKD in cART-naïve populations, and recent studies have suggested that the renal benefits of cART in sub-Saharan Africa are similar to that observed in the US population.[40,41,50] At the same time, there are limited data about potential adverse sequelae of long-term cART exposure in resource-poor settings with less intensive monitoring.

CONCLUSIONS

With changes in the epidemiology of HIV infection and HIV-related kidney disease, health-care providers in the US and Europe will be expected to manage an aging HIV-infected population with comorbidities such as diabetes, hypertension, HCV, and CKD. The more indolent course of HIV-related kidney disease in cART-treated patients and the high prevalence of comorbid CKD will make early diagnosis and subsequent management challenging. In contrast, HIVAN remains a prominent threat to the health of HIV-infected individuals in sub-Saharan Africa, where genetic susceptibility to CKD is common and resources for the diagnosis and management of chronic diseases are limited. With substantial genetic heterogeneity across Africa, local estimates of CKD prevalence and disease spectrum are needed to determine the proper allocation of resources for CKD screening and management in HIV-infected individuals. Although international guidelines consider cART first-line therapy for HIVAN, the role of cART in non-HIVAN CKD should be evaluated in future studies. In both resource-rich nations and in Africa, the contribution of comorbid CKD risk factors to HIV-related kidney disease and the potential for HIV and cART to accelerate the course of comorbid CKD should also be investigated.

DISCLOSURE

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