HIV and the Kidney: A Spotlight on Racial Disparities

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In 1984, physicians at a New York City hospital described an aggressive form of kidney disease affecting 12% of their patients with AIDS [1]. Progression to end-stage renal disease (ESRD) was nearly universal, and all affected patients were African American or Haitian immigrants. Subsequent studies have consistently demonstrated a strong association between black race and this unique form of kidney disease, now recognized as HIV-associated nephropathy (HIVAN) [2–4]. In the United States, African Americans account for nearly 90% of the incident ESRD attributed to HIVAN [5], a racial predisposition rivaling that associated with sickle-cell nephropathy [6]. Because these data are based primarily on clinical diagnoses, it is likely that many cases of ESRD that are attributed to HIVAN actually reflect a broader spectrum of HIV-related and comorbid kidney diseases [4, 7]. Until recently, the impact of race on these other forms of HIV-related kidney disease has not been well understood.

Several recent publications have highlighted the significant influence of race on the epidemiology of chronic kidney disease (CKD) in HIV-infected patients, regardless of the underlying pathology [8–11]. Although decreased kidney function was identified in <5% of the largely white EuroSIDA cohort [8], cross-sectional data from a New York City HIV clinic demonstrated a high prevalence of kidney disease in minority patients, including ESRD in 4% and pre-end-stage CKD in >11% of patients [9]. In addition to this striking disparity in prevalence, investigators from the US Veterans Affairs Medical System have recently described racial differences in the incidence and progression of HIV-related kidney disease [10]. Although the baseline prevalence of decreased kidney function was similar in HIV-infected veterans regardless of their race, the incidence of ESRD was nearly 6-fold higher in HIV-infected African Americans. HIVAN was the most common cause in African Americans. HIVAN was the most common presumed diagnosis, but more than half of the cases of ESRD were attributed to another etiology [10]. In a smaller cohort of veterans who had preexisting kidney disease, the rate of progression in HIV-infected African Americans was similar to that observed in patients with diabetes [11].

In this issue of the Journal, Lucas et al. describe the impact of race on the epidemiology of CKD in the Johns Hopkins HIV Clinical Cohort [12]. The findings of their study are consistent with those arising from the study of the Veterans Affairs cohort [10] and suggest that the disproportionate burden of ESRD in HIV-infected African Americans is primarily attributable to a more-rapid progression of kidney disease. Although the incidence of CKD was only slightly increased in African American participants compared with white participants, the risk of progression to ESRD was 18-fold higher. In a subgroup of patients, for whom kidney-biopsy data were available, African Americans were significantly more likely to progress to ESRD, regardless of the etiology of kidney disease, suggesting that the observed racial disparity is not unique to HIVAN.

The incidence of ESRD in whites in the Johns Hopkins cohort was actually so low that Lucas et al. were unable to adjust for other demographic and clinical characteristics that could confound the relationship between race and the progression of kidney disease; however, it is reassuring that similar results were observed in the larger Veterans Affairs cohort after adjustment for age, sex, baseline kidney function, comorbid conditions, and socioeconomic status. Notably, fewer than one-tenth of HIV-infected veterans were women, compared with nearly one-third of the participants in the Johns Hopkins cohort. The impact of sex on the risk for progression of kidney disease should be the subject of further study in other patient cohorts, particularly because Lucas et al. have identified female sex as a risk factor for incident kidney disease but not for ESRD [12, 13].

Although the inclusion of data from a single institution or hospital network may limit the generalizability of these recent studies, single- and multicenter cohorts are increasingly important resources for
the study of HIV-related kidney disease. Previous studies of HIV-related ESRD often relied on data from the US Renal Data System, a federally funded database that collects demographic and clinical information on all patients who start chronic dialysis or receive a kidney transplant [5]. The database continues to collect information on patients with a primary diagnosis of “AIDS nephropathy” but, because of state confidentiality laws, no longer collects data on the prevalence of comorbid HIV/AIDS. As a result, nationally representative estimates are available only for patients with ESRD attributed to HIVAN, and the true prevalence of HIV-related ESRD is unknown.

Lucas et al. recently demonstrated the continued utility of this national database to identify or confirm ESRD events in established HIV cohorts [13]. Combining data from the Johns Hopkins HIV cohort and from HIV-positive participants in the AIDS Link to the IntraVenous Experience (ALIVE) cohort, Lucas et al. demonstrated a 31-fold increase in the risk of ESRD in African-Americans, compared with that in whites. Consistent with the findings reported by Lucas et al. in this issue, the incidence of HIV-related ESRD was similar in the periods before and after the introduction of combination antiretroviral therapy (ART), regardless of the regimen used and despite a decline in the incidence of earlier stages of CKD [13]. As Lucas et al. report in this issue, these data may suggest a role for earlier initiation of ART in high-risk patients, prior to the establishment of kidney disease. This recommendation goes beyond the recently updated treatment guidelines, which now recommend the initiation of ART in patients with HIVAN, regardless of CD4 cell count [14], and is even more sweeping than the Infectious Diseases Society of America’s recommendations to consider ART in all patients with HIV and CKD [15].

The current guidelines are based on expert opinion and strong observational data, in the absence of rigorous prospective trials, and the impact that ART has on other forms of HIV-related kidney disease is less clear [4]. The National Institutes of Health–funded Strategic Timing of Antiretroviral Treatment (START) Study is expected to begin enrollment later this year and will investigate the impact of early initiation of ART (at CD4 counts >500 cells/mm³, compared with deferral of ART to a CD4 count of 350 cells/mm³), on AIDS and non-AIDS events, including kidney disease. While awaiting the results of this large international randomized trial, HIV providers should focus on the identification of early CKD in patients at high risk for progression, including African Americans and patients with a family history of ESRD. The results presented by Lucas et al. also provide further support for the use of angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers in these patients [12], in addition to individualized consideration of ART.

Beyond the implications for individual patient care, the observed racial disparities in HIV-related ESRD have significant implications for global public health. In the United States, the prevalence of ESRD attributed to HIVAN continues to increase, the result of improved survival in the ART era and continued growth of the population at risk [5]. The potential implications for sub-Saharan Africa are even more staggering, particularly in light of the limited infrastructure for identification and management of kidney disease and ESRD. Emerging data suggest that the prevalence of HIV-related kidney disease in African populations is similar to that observed in African Americans. In a South African study, 7% of HIV-positive patients without overt kidney disease were found to have proteinuria on screening [16], whereas dipstick proteinuria was identified in 21% of ART-naive patients in Uganda [17]. More than 40% of patients in the Ugandan study had an estimated creatinine clearance <50 mL/min [17], and similar findings were reported in a small study from Nigeria, where the median creatinine clearance was <60 mL/min [18]. In a larger Nigerian study, 38% of HIV-infected patients had some evidence of kidney disease, defined by the presence of proteinuria and/or elevated levels of serum creatinine [19].

Interpretation of these findings is complicated by the lack of validated estimates of glomerular filtration in these populations. The 2 most commonly used estimation equations provided remarkably different estimates of the prevalence of decreased kidney function in ART-naive ambulatory patients in Kenya (11.5% vs. 4.8%), despite reasonable overall correlation between the equations [20]. Accurate and reliable identification of patients with decreased kidney function is essential to guide selection of ART dosing and regimen, particularly in resource-limited settings where close monitoring of toxicity is not feasible. In light of the potential for an epidemic of HIV-related kidney disease and ESRD in disadvantaged minority populations and in Africa, the international medical community should work to develop simple, inexpensive, and reliable methods to detect and manage early kidney disease in these vulnerable populations.

References