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Absence of HIV-Associated Nephropathy Among Antiretroviral Naive Adults With Persistent Albuminuria in Western Kenya

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Introduction: HIV-associated nephropathy (HIVAN) has been strongly linked to African ancestry. However, studies have demonstrated wide variability in the prevalence of HIVAN in different sub-Saharan African populations. Accurate assessment of the disease burden is important because antiretroviral therapy (ART) is increasingly available and may prevent progression to end-stage renal disease.

Methods: We prospectively screened ART-naïve, afebrile, nonhypertensive, and nondiabetic adults attending a large HIV care program in Western Kenya for the presence of albuminuria (dipstick albumin $\geq$ trace or urine albumin to creatinine ratio (UACR) $\geq$ 30 mg/g). Those with albuminuria confirmed on 2 occasions, subject to consent, underwent kidney biopsy.

Results: Among 523 subjects screened, 85 (16.3%) had albuminuria on the initial screen, and persistent albuminuria was confirmed in 32 of the 53 (60%) who returned for confirmatory testing. A total of 27 subjects with persistent albuminuria underwent biopsy. The median age was 34 years (interquartile range [IQR] 30–42 years), and 63% were female. The median CD4 count was 369 cells/μl (IQR 89–492 cells/μl). Renal function was normal in 92%. Median UACR was 257.5 mg/g (IQR 93.5–543 mg/g), and 92% had UACR $<$ 1 g/g. No subject had histologic features consistent with HIVAN; 41% had acute interstitial nephritis (AIN); 33% had nonspecific findings, and 2 patients had arteriosclerosis. Focal segmental glomerulosclerosis, acute postinfectious glomerulonephritis, chronic interstitial nephritis, pyelitis, and papillary sickling were seen in 1 patient each.

Discussion: Among ART-naïve adults with persistent albuminuria at a referral center in Western Kenya, we observed no cases of HIVAN. AIN was the most common cause of persistent proteinuria in this setting.

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Sub-Saharan Africa is disproportionately affected by the human immunodeficiency virus (HIV). In 2013, 24.7 million of the 35 million persons living with HIV/AIDS worldwide were in sub-Saharan Africa, and 73% of all AIDS-related deaths occurred there. Kenya is home to the fourth largest population of persons living with HIV, an estimated 1.4 million individuals aged 15 years and over. Only approximately 35% of them are on combination antiretroviral therapy (ART).[1,2]

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HIV infection has been associated with kidney disease, especially among individuals of African descent. HIV-associated nephropathy (HIVAN) is the classic cause of kidney disease in HIV, and is a leading cause of chronic kidney disease and end-stage renal disease (ESRD) in populations with limited access to ART.[3–10] Before the use of ART, HIVAN typically led to ESRD within months, with a mortality of close to 100% in 6 months.[9,11,12] The histopathology of HIVAN is characterized by focal segmental glomerulosclerosis (FSGS) with glomerular collapse, tubular microcysts, and interstitial inflammation.[9,13–15]

Studies have identified a genetic susceptibility locus on chromosome 22 that explains the increased risk of HIVAN and other forms of nondiabetic kidney disease in individuals of African descent.[16,17] Despite the

strong association with African ancestry, data on HIV-related kidney diseases and HIVAN among native African populations are scarce and widely varied. In South Africa, studies have varied by geographic locale, with estimates of HIVAN prevalence ranging from <5% of biopsy results in HIV-positive individuals in the Johannesburg area to as high as 83% of those with persistent proteinuria in KwaZulu Natal[18–22] In West Africa, 1 study from Nigeria reported HIVAN in 7 of 10 HIV-positive subjects with proteinuria who underwent kidney biopsy.[23] In contrast, prior studies have suggested a lower prevalence of HIVAN in East Africans, although these studies did not include biopsy confirmation. Among 126 Ethiopian Israelis with HIV infection who were examined for the presence of proteinuria and/or reduced glomerular filtration rate (GFR) as evidence of HIVAN, none fulfilled these criteria.[24] A study in the same setting as the present study screened 373 ART-naïve HIV-positive Kenyan adults and identified dipstick proteinuria of ≥1+ in only 6.2%.[25]

Other kidney diseases have been described in association with HIV infection. Acute kidney injury is common, and may be secondary to infections, hypotension, and nephrotoxic medications, including antibiotics, antiretroviral agents, and herbal medicines.[3,5] Acute interstitial nephritis may also occur secondary to drugs, including those used to treat opportunistic infections.[26] HIV-associated immune complex kidney disease (HIVICK) is increasingly recognized,[5,11,18,19,27–33] and other lesions that have variably been associated with HIV infection include membranoproliferative glomerulonephritis, minimal change disease, membranous glomerulopathy, amyloidosis, and IgA nephropathy.[7,19]

The current study was designed to estimate the prevalence of HIVAN among HIV-positive, ART-naïve adults with persistent proteinuria seeking care at a large HIV care program in Western Kenya. We also sought to determine what other histological variants of kidney disease were identifiable in this population.

MATERIALS AND METHODS

This was a cross-sectional study among HIV-positive, ART-naïve adults attending the clinics of the Academic Model Providing Access to Healthcare (AMPATH) program based at the Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya. Subjects with fever, hypertension, diabetes, heart disease, or documented ESRD were excluded. All subjects provided written informed consent, and the study was approved by the Institutional Research and Ethics Committee of MTRH and Moi University School of Medicine.

At the first visit, all eligible participants were subjected to a routine urine dipstick test for the detection of protein (Uriscan, YD Diagnostics). If negative, a semiquantitative microalbumin dipstick test (Clinitek 50 microalbumin analyzer, Bayer Healthcare and Clinitek Microalbumin 2 strips, Siemens Healthcare Diagnostics) was performed, and if both were negative, subjects were excluded from further testing. Subjects with a positive result on either the routine urine dipstick test for protein or the microalbumin dipstick had a confirmatory dipstick test performed in a period of no less than 2 weeks. Persistent albuminuria was defined as the presence of dipstick protein ≥ trace or semi-quantitative urine albumin: creatinine ratio (UACR) ≥ 30 mg/g on 2 occasions at least 2 weeks apart. Basic demographic data, CD4 cell count, and serum creatinine were abstracted from the clinic chart where available. HIV viral load testing is not performed as standard of care in ART-naïve adults in the AMPATH program.

Among subjects with persistent albuminuria who consented to kidney biopsy for research purposes, additional data on demographics, family history of kidney disease, current medications, and current symptoms were collected by interview, and a focused physical examination was performed. Serum creatinine (standardized Jaffe alkaline picrate reaction, Roche COBAS Integra 400 Plus), CD4 cell count (BD FACSCalibur flow cytometer), and a formal UACR (Roche COBAS Integra 400 Plus) were measured in the AMPATH clinical laboratory. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR).[34] A bleeding time and renal ultrasound were performed, and a percutaneous kidney biopsy was performed if not contraindicated. Formalin-fixed biopsy samples were processed into paraffin blocks, and de-identified tissue blocks were sent for analysis by a single renal pathologist (VDD). Histopathologic analysis was limited to light microscopy only. Slides were stained with hematoxylin and eosin (H&E), periodic acid—Schiff, and Mason's Trichrome stains.

Data were summarized as medians and proportions, and the Fisher exact test was used to test for associations. A P value of 0.05 was considered statistically significant.

RESULTS

A total of 523 eligible subjects were screened (Figure 1). All screened subjects were black/indigenous Africans. Among 431 subjects with data available in the clinic chart, the median age was 35 years (IQR 30—41), and 73% were women. The median CD4

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