

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/ μ l (IQR 89–492 cells/ μ l). 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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KEYWORDS: Chronic kidney disease; Epidemiology; Focal segmental glomerulosclerosis; HIV-associated nephropathy; HIV-related kidney diseases; Kenya

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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}

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

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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 $\geq 1+$ 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, hypertension, 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, Kyunggi-Do, Korea). If negative, a semiquantitative microalbumin dipstick test (Clinitek 50 microalbumin analyzer, Bayer Healthcare [Elkhart, Indiana] and Clinitek Microalbumin 2 strips, Siemens Healthcare Diagnostics [Deerfield, Illinois]) 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 \geq 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 Masson'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 cell count was 418 cells/ μl (IQR 283–558), and only 12% had CD4 cell counts < 200 cells/ μl . Only 2.6% had an eGFR < 60 mL/min/1.73 m². Overall, 85 (16.3%) subjects had albuminuria on the initial screening dipstick examination; all of these subjects were invited to return for confirmatory testing. Among 53 subjects with albuminuria on the initial test who returned for repeat testing, 32 (60%) had persistent albuminuria based on the dipstick test for urine protein or semi-quantitative microalbumin. In all, 28 of these subjects consented to kidney biopsy; 1 participant with hypertension was excluded from further analysis (Table 1).

Of the 27 eligible subjects who underwent kidney biopsy, 17 were female, and the median age was 34 years (IQR 30–42 years). Only 1 subject reported a family history of kidney disease. The majority of subjects who underwent kidney biopsy (78%) were asymptomatic. Fourteen subjects (52%) reported current medication use. The most common medications were trimethoprim/sulfamethoxazole and amoxicillin ($n = 5$ each). Others included antituberculosis drugs ($n = 2$), multivitamins ($n = 2$), and 1 report each of dapson, paracetamol, ibuprofen, indomethacin, metronidazole, and fluconazole.

The majority of subjects who consented to kidney biopsy (85%) had normal physical examination findings. None were hypertensive and none had edema. Abnormal examination findings included minor mucosal and skin findings. The median CD4 cell count was 369 cells/ μl (IQR 89–492 cells/ μl), and only one-third had CD4 counts < 200 cells/ μl . The estimated GFR was < 60 ml/min/1.73 m² in only 2 of the 27 subjects who underwent kidney biopsy, 1 subject with an eGFR of 20 ml/min/1.73 m² and a second with an eGFR of 49 ml/min/1.73 m². The median UACR was 257.5 mg/g (IQR 93.5–543 mg/g), and only 2 subjects had proteinuria > 1 g/g (Supplementary Table S1).

None of the biopsy samples had features diagnostic of HIVAN, including collapsing FSGS or tubular microcysts. The most common diagnosis, in 11 participants (41%), was acute interstitial nephritis (AIN). Both subjects with an eGFR < 60 ml/min/1.73 m² had AIN on biopsy, and 1 of the 2 subjects with UACR > 1 g/g had mixed AIN and acute postinfectious glomerulonephritis. In all, 33% of the subjects had nonspecific findings, including the second participant with UACR > 1 g/g. Other diagnoses included 2 cases of arteriosclerosis and 1 case each of noncollapsed FSGS, chronic interstitial nephritis, pyelitis, and papillary sickling consistent with sickle cell nephropathy (Figure 2 and Supplementary Table S2). Using the Fisher exact test, no association was found between

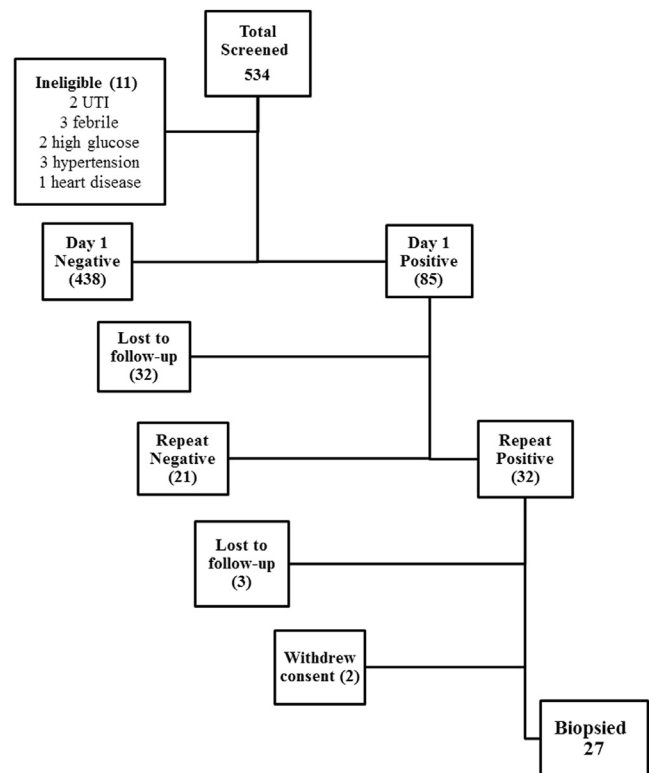


Figure 1. Recruitment summary. UTI, urinary tract infection.

age, sex, tribe, or CD4 count and the respective diagnoses.

Further review of the AIN cases demonstrated no eosinophils to suggest allergic or drug-induced AIN. In addition, none of the AIN cases had a predominant ($> 50\%$) plasma cell infiltrate. All of the cases with plasma cells exhibited an admixture of other leukocytes, including lymphocytes and in some cases neutrophils. There was no evidence of diffuse infiltrative lymphocytosis syndrome, which can occur in the setting of untreated HIV infection.

DISCUSSION

In this cross-sectional study of ART-naïve adults in Western Kenya, persistent albuminuria was rare, and there were no features consistent with a diagnosis of HIVAN among 27 individuals with persistent albuminuria who underwent kidney biopsy.

An earlier study done in South Africa showed that HIVAN can occur at a very early stage of HIV, and this informed the decision to biopsy this population.¹⁹

The absence of HIVAN in our sample is consistent with earlier studies among East African populations, which demonstrated a very low prevalence of proteinuria in HIV-positive adults,^{24,35} and with available data on genetic susceptibility to kidney disease in different African populations. Genome-wide association studies have identified polymorphisms in the gene *APOL1* as important contributors to the increased

Table 1. Clinical characteristics and histologic diagnoses of antiretroviral-naïve Kenyan adults with persistent albuminuria (N = 27)

	n or Median (IQR)
Age, yr	34 (30–42)
Female sex	17
Tribe	
Luo	10
Kalenjin	8
Kikuyu	5
Luhya	4
Family history of kidney disease	1
On at least 1 medication	14
CD4 cell count, cells/ μ l	369 (89–492)
CD4 cell count <200 cells/ μ l	9
eGFR, ml/min/1.73 m ²	108.7 (87.1–126.9)
eGFR <60 ml/min/1.73 m ²	2
UACR, mg/g	257.5 (93.5–543)
UACR >1 g/g	2/26
Histology	27
HIVAN	0
AIN	11
Nonspecific findings	9
Arteriosclerosis	2
Noncollapsing FSGS	1
Postinfectious glomerulonephritis with AIN	1
Chronic interstitial nephritis	1
Pyelitis	1
Papillary sickling/sickle cell nephropathy	1

AIN, acute interstitial nephritis; eGFR, estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; IQR, interquartile range; UACR, urine albumin:creatinine ratio.

risk of HIVAN, primary FSGS, and hypertensive kidney disease in individuals of African descent.¹⁷ Available data suggest that populations in East Africa have a lower frequency of these genetic variants (4.5%–7% in Kenya compared to up to 21% in South Africa and 45% in Nigeria) and thus may be less likely to develop these diseases.³⁶ The discrepancy between our study findings and that of Han *et al.*¹⁹ in South Africa is noteworthy, and is likely due to the difference in genetic makeup between the 2 populations. While the study design was similar, they reported an 83% overall prevalence of HIVAN. Among 7 subjects with microalbuminuria, 6 had evidence of HIVAN suggesting that early diagnosis of HIVAN was possible. It is also notable that the screened population was relatively healthy, with only 12% having a CD4 cell count < 200 cells/ μ l and with no comorbid diabetes and hypertension.

AIN was the predominant diagnosis in the current study. The study was originally designed to determine the prevalence of HIVAN, and these findings were not anticipated. For the same reason, other urinary findings such as pyuria, hematuria, and glycosuria were not rigorously recorded at the time of the screening visit. The most common etiology of AIN is medications.

Other causes include infections, tubulointerstitial nephritis and uveitis (TINU) syndrome, and sarcoidosis.³⁷ In the current study, 45% of the subjects with a histologic diagnosis of AIN reported using at least 1 medication. Common medications associated with AIN include penicillins, sulfonamides, and analgesics; these were also the most frequently reported medications in our population. Another possible cause of AIN is the use of herbal medicines, many of which have been associated with interstitial nephritis. In developing nations, use of traditional medicine for primary health care approaches 80%.³⁸ The current study did not rigorously investigate herbal medication use.

Although the absence of eosinophils in the cases examined does not exclude the possibility of drug-induced AIN, it is possible that AIN was caused by HIV infection or by endemic infections, a question that this study was not designed to answer.³⁹ There are no local data on specific endemic infections associated with AIN. As discussed by Wearne *et al.*,²² there is a possibility that in some patients the interstitial inflammatory infiltrate is a manifestation of HIV infection; however, none of our cases had the characteristically predominant (>50%) plasma cell infiltrate. Differential diagnosis would also include other infectious etiologies (such as bacterial pyelonephritis). The etiology of the necrotizing, non-caseating granuloma identified in one case could not be determined as no fungal organisms were identified with periodic acid-Schiff (PAS) stain, and stain for acid fast bacilli (AFB) was not available. Podocyte abnormalities could not be conclusively described, as we did not have electron microscopy to evaluate the degree of foot process effacement. The presence of podocyte swelling by light microscopy is not specific and could vary with hyperfiltration states and fixation conditions.

This study was limited by the inability to elucidate the causes of AIN and nonspecific renal inflammation that were the predominant histological findings. The histopathological analysis was also restricted to light microscopy, and we may have missed subtle cases of HIV immune complex kidney disease. No typical ball-in-cup phenomenon was identified with special stains, although this possibility would require electron microscopy for more definitive identification. By light microscopy, the findings in the single case with acute glomerulonephritis suggested typical humps as seen in infection-related glomerulonephritis. There was also significant loss to follow up between the 2 screening visits and the biopsy, limiting our ability to provide quantitative estimates of the prevalence of proteinuria and HIVAN. Data on the prevalence of proteinuria in the local HIV population are available from a previous study in the same setting,²⁵ and the focus of the

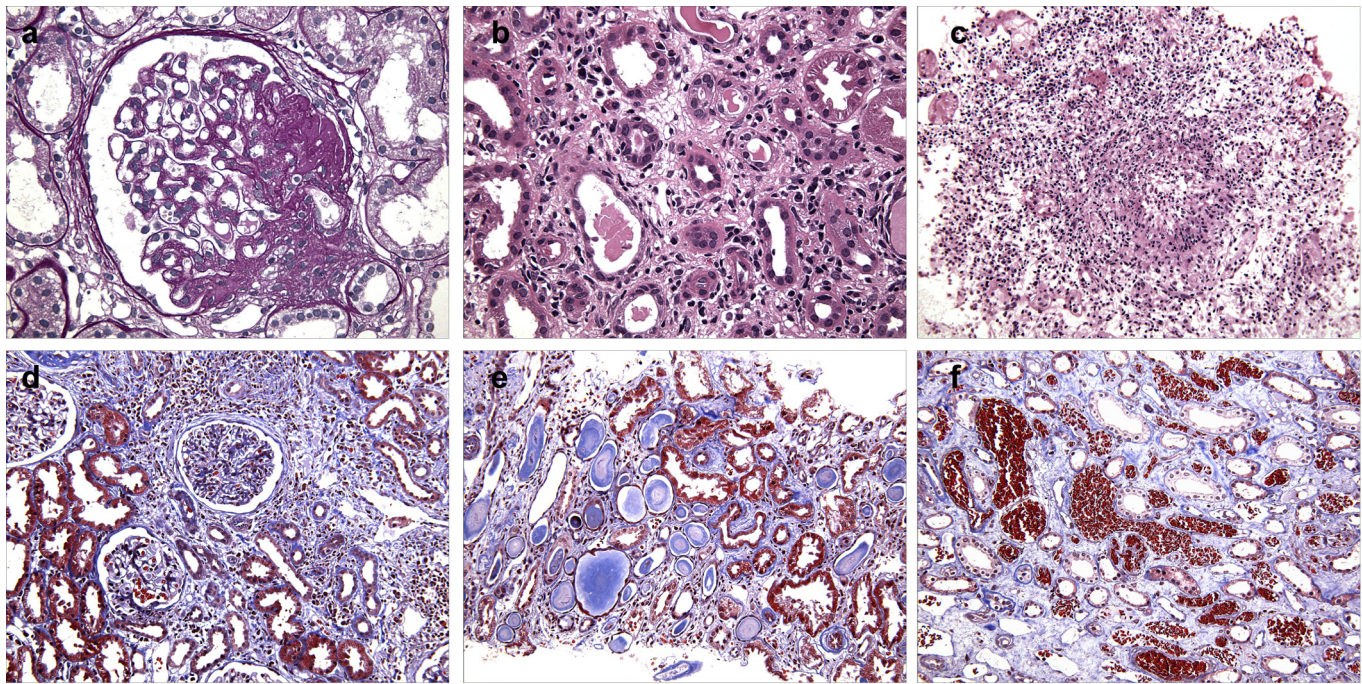


Figure 2. Representative kidney histology in antiretroviral-naïve adults with persistent low-grade albuminuria. (a) Case 4: Focal segmental glomerulosclerosis, perihilar variant, periodic acid–Schiff (PAS), original magnification $\times 400$. Characteristic features of HIV-associated nephropathy, including glomerular collapse, proliferation of glomerular epithelial cells, and microcystic tubular dilatation, are not seen. (b) Case 16: Acute interstitial nephritis (AIN), showing interstitial inflammation by mononuclear leukocytes, tubulitis, edema, and acute tubular injury, hematoxylin and eosin (H&E), original magnification $\times 400$. (c) Case 21: AIN with necrotizing granuloma, H&E, original magnification $\times 200$. (d) Case 16: Chronic interstitial nephritis, showing chronic inflammation, tubular atrophy, and interstitial fibrosis with preservation of glomeruli, Trichrome, original magnification $\times 200$. (e) Case 19: Chronic interstitial nephritis, showing tubular thyroidization with regular hyaline casts and interstitial fibrosis, Trichrome, original magnification $\times 200$. (f) Case 26: Red blood cell sickling in distended *vasa recta* of the medulla, Trichrome, original magnification $\times 200$.

current study was to describe the underlying kidney disease among individuals with persistent low-grade proteinuria. This study was set in a center with advanced HIV care and potentially, although unlikely, subjects with more advanced HIV and higher risk of HIVAN could have been overlooked.

The current study suggests that the prevalence of HIVAN among HIV-positive, ART-naïve adults in Western Kenya is very low. The prevalence of persistent albuminuria was low, and those with persistent albuminuria were more likely to have AIN or nonspecific findings. Genetic differences between this population and other populations in sub-Saharan Africa may explain the differences in kidney disease epidemiology in this and other settings in Africa. Our findings do not have a significant impact on the current standard of care of HIV-positive patients in Western Kenya, where kidney biopsy is not universally available and where ART is now recommended for all patients regardless of CD4 cell count. We would encourage urine dipstick testing and thorough evaluation of patients with urinary abnormalities, including the discontinuation of any nonessential medications or supplements that could be contributing to AIN. Further studies should evaluate the causes of AIN and nonspecific renal inflammation

that are common among HIV-positive adults with persistent, low-grade albuminuria in this setting.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Summary of clinical findings (N = 27).

Table S2. Biopsy results.

Supplementary material is linked to the online version of the paper at <http://www.kireports.org>.

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