

Predictors and Prognosis of HIV-Associated Nephropathy on Kidney Biopsy in South Africa



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Introduction: South Africa has the highest prevalence of HIV in the world. The epidemiology of kidney disease among people with HIV infections is well-described in the United States. However, there are limited data coming from South Africa, particularly that involve kidney biopsies. The purpose of this study was to determine what, if any, patient factors are predictive of HIV-associated nephropathy (HIVAN) on kidney biopsy in a South African kidney biopsy cohort.

Methods: This study prospectively collected data of all patients infected with HIV referred to the Groote Schuur Hospital (GSH) renal unit for a kidney biopsy from 2002 to 2018.

Results: There were 419 patients included in the study. Mean age was 36.5 years (SD, 9.4); 219 (52.3%) were women; and all were black. Seventy-nine patients (18.9%) were on dialysis at the time of biopsy; the mean estimated glomerular filtration rate among the remainder was 41.4 ml/min per 1.73 m² (SD, 39.2). Only 163 patients (47.1%) were known to be taking antiretroviral therapy (ART) at the time of biopsy. There were 246 (58.7%) cases of HIVAN detected, and they were comparable on age, sex, kidney function, and kidney size to those with kidney disease of other causes but were less likely to be taking ART ($P < 0.001$). Biopsy confirmed HIVAN was associated with mortality (adjusted hazard ratio, 1.77; 95% confidence interval [CI]: 1.07–2.91; $P = 0.025$), and the use of ART at biopsy was protective (adjusted hazard ratio, 0.52; 95% CI, 0.32–0.84, $P = 0.008$). The proportion of HIVAN on biopsy decreased and the proportion taking ART increased from 2002 to 2018 (P for trend for both < 0.001).

Conclusion: In summary, HIVAN was the most common etiology of kidney disease in this biopsy cohort from South Africa; however, the proportion with biopsy-proven HIVAN declined over time, perhaps in the setting of greater ART availability.

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KEYWORDS: antiretroviral therapy; HIVAN; kidney biopsy; South Africa

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South Africa has the highest number of people living with HIV in the world.^{1,2} Initial governmental responses to treating people who are HIV-positive were regrettably suboptimal until 2003.^{3,4} Since then, there has been significant progress in the public health policy, with informed efforts to address the global public health problem. South Africa now has the largest ART program in the world. As a result, the

quality of life and life expectancy of South Africans who are HIV-positive has increased.⁵

However, with every profit comes a cost. While HIV-seropositive people are living longer, the development of chronic disease (HIV-associated and otherwise) has also increased. One common comorbidity among HIV-positive people is kidney disease. In the absence of combined ART (cART), HIVAN represents an important cause of morbidity and mortality in those with advanced HIV seropositivity.⁶ Unfortunately, the definitive diagnosis of HIVAN is made by obtaining a kidney biopsy specimen, a procedure that carries complication risks to the patient and is not widely available in many countries in Africa.⁷ Thus, whether the prevalence of HIVAN

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has declined over time with greater availability of ART has not been described.

GSH is a tertiary academic care centre in Cape Town, South Africa. GSH is one of the few centers to perform and have a kidney biopsy registry, serving a population of approximately 5.8 million people. In 2015, an estimated 85% of HIV-seropositive adults in the South African population were diagnosed; 57% of those diagnosed were on cART, and 78% of those on cART were virally suppressed.⁸ The purpose of this study was to 1) describe kidney histology in South Africans treated at GSH who are HIV-positive; 2) estimate the prevalence of HIVAN in this group and whether it has changed over time; 3) identify clinical characteristics that correlate with the prevalence of HIVAN on biopsy; and 4) determine whether HIVAN confers a different prognosis compared with other kidney disease etiologies.

METHODS

Study Population

We sought to include all HIV-positive patients who were referred to the GSH Renal Unit for a kidney biopsy procedure. The GSH Renal Unit has an active outpatient and consultative service, including but not limited to outpatient clinics for transplant follow-up, patients with HIV-associated kidney disease, and adolescent patients. The GSH Renal Unit is also responsible for all patients with acute kidney injury in the hospital and approximately 155 patients on chronic outpatient dialysis—100 on hemodialysis and 55 on peritoneal dialysis. Based on clinical records and the kidney biopsy registry, there were 464 patients diagnosed with HIV referred for kidney biopsy procedures between 2002 and 2018. Patients who had data missing on age and sex were excluded.

Institutional ethical approval was obtained from the University of Cape Town Human Research Ethics Committee to access the data; institutional review board approval was also obtained from the Johns Hopkins Bloomberg School of Public Health.

Outcomes and Covariates

The primary outcomes evaluated were biopsy-proven HIVAN and death. HIVAN was diagnosed according to the pathologic classification of HIV-related kidney diseases established by the Kidney Disease: Improving Global Outcomes controversies conference.⁹ All biopsy specimens were reviewed by a single pathologist and discussed in a conference with the pathologist and 4 consultant nephrologists. For this study, any biopsy procedure performed before the Kidney Disease: Improving Global Outcomes publication was rereviewed by the pathologist and a consultant

nephrologist to ensure consistency. Death was recorded based on the clinical records.

To assess kidney function and to standardize the units of measurement with norms in the United States, serum creatinine values were converted from mmol/l to mg/dl for use in the estimated glomerular filtration rate equation put forth by the Chronic Kidney Disease Epidemiology Collaboration formula and expressed in ml/min per 1.73 m², with application of the factor 1.159 for black ethnicity.⁵¹

We evaluated the following variables at the time of the kidney biopsy procedure: age, sex, race, blood pressure, hepatitis B status, hepatitis C status, HIV parameters (viral load and CD4 count), use of cART, estimated glomerular filtration rate, urine protein/creatinine ratio, hemoglobin, dialysis status, and kidney size on ultrasound. Availability of data are shown in [Supplementary Table S1](#).

Statistical Analyses

We described the baseline characteristics of the study cohort and grouped them by HIVAN and cART status, testing differences using chi-square tests for categorical variables and analysis of variance for continuous variables. Logistic regression was performed to assess for multivariable associations between demographic and clinical characteristics with the diagnosis of HIVAN on kidney biopsy. The primary model included age, sex, mean kidney size, use of cART, albumin, and hemoglobin. Among patients who did not require dialysis at the time of the biopsy procedure, we also evaluated the urine protein/creatinine ratio as a predictor of HIVAN. Kaplan–Meier plots were used to show the time to death by HIVAN and cART status. Cox proportional hazards regression was used to assess the adjusted association with risk of mortality. Models included age, sex, dialysis status, hemoglobin, albumin, cART, HIVAN, and CD4 count. Missing covariates were imputed using multiple imputation.

RESULTS

Study Population

There were 419 patients in the study population, which was 100% black and 52.3% female, with a mean age (SD) of 36.5 (9.4) years ([Table 1](#)). At the time of the biopsy procedure, systolic and diastolic blood pressure (SD) was 130 (26.4) mm Hg and 79 (18.1) mm Hg, respectively. The average kidney size (SD) on ultrasound was 12.7 (8.4) cm. Excluding the 79 patients who were already on dialysis at the time of the biopsy procedure, the mean estimated glomerular filtration

Table 1. Baseline characteristics at time of biopsy, by presence of HIVAN

Variable	Overall	No HIVAN; no cART	No HIVAN; cART	HIVAN; no cART	HIVAN; cART	P value
N	419	44	58	136	97	
Age at biopsy, yr	36.5 (9.4)	35.4 (8.7)	37.4 (9.1)	35.0 (9.5)	37.2 (9.2)	0.208
Female (%)	219 (52.3)	22 (50.0)	31 (53.4)	74 (54.4)	51 (52.6)	0.964
Blood pressure, mm Hg						
Systolic	129.8 (26.4)	133.6 (25.4)	131.6 (27.7)	130.4 (30.4)	125.8 (21.3)	0.402
Diastolic	79.2 (18.1)	79.2 (17.7)	78.3 (19.6)	81.4 (21.0)	77.8 (13.8)	0.528
Ultrasound measurements, cm						
Right kidney length	12.5 (7.8)	12.1 (1.4)	14.0 (13.3)	11.9 (1.6)	12.9 (11.7)	0.552
Left kidney length	13.0 (9.9)	15.1 (17.4)	14.3 (14.1)	12.1 (2.5)	12.9 (11.6)	0.443
Biochemistry and serology						
Hemoglobin, g/dl	9.4 (8.0)	8.7 (2.4)	9.1 (2.0)	10.3 (13.1)	9.0 (2.0)	0.581
Albumin, g/dl	2.8 (1.0)	2.7 (0.8)	2.9 (0.8)	2.5 (1.1)	3.1 (0.8)	0.002
Serum creatinine, mg/dl ^a	2.8 (1.4–6.4)	3.1 (1.1–6.2)	2.9 (1.2–6.7)	2.4 (1.3–6.1)	2.5 (1.4–5.1)	0.351
eGFR, ml/min per 1.73 m ^{2a}	26 (10–63)	29 (10–83)	23 (9–73)	32 (12–73)	33 (14–63)	0.770
Urine protein creatinine ratio, g/g ^a	0.3 (0.1–0.7)	0.2 (0.1–0.5)	0.2 (0.1–0.2)	0.4 (0.2–0.9)	0.3 (0.2–0.6)	0.616
Viral load, log-1010 copies/ml	2.7 (2.3)	4.3 (0.7)	1.7 (2.2)	3.9 (1.8)	2.0 (1.9)	<0.001
CD4 count, cells/mm ³	232.5 (216.9)	279.9 (238.2)	227.2 (239.7)	235.6 (215.7)	198.9 (190.8)	0.252
Limb edema (%)	109 (36.6)	11 (34.4)	17 (39.5)	40 (38.1)	26 (33.8)	0.897
Hepatitis B status (%)	79 (23.8)	14 (35.0)	13 (26.5)	31 (27.7)	13 (15.9)	0.099
Hepatitis C status (%)	30 (9.7)	1 (2.7)	6 (12.8)	7 (6.7)	12 (16.0)	0.075
Treatment status						
Dialysis (%)	79 (23.8)	14 (35.0)	13 (26.5)	31 (27.7)	13 (15.9)	0.099
Antihypertensives (%)	118 (40.5)	12 (32.4)	26 (55.3)	44 (35.5)	35 (44.3)	0.071

cART, combined antiretroviral therapy; eGFR, estimated glomerular filtration rate; HIVAN, HIV-associated nephropathy.

^aMedian (interquartile range).

All values are mean (SD) or *n* (%) unless otherwise noted.

rate was 41.4 ml/min per 1.73 m². Only 163 (47.1%) patients were on cART.

Association Between Covariates With HIVAN

Of 419 patients, 246 (58.7%) had biopsy-confirmed HIVAN. The most common non-HIVAN causes were immune complex disease (*n* = 38), granulomatous interstitial nephritis (*n* = 18), and acute tubular necrosis (*n* = 13). When evaluating baseline and clinical characteristics, patients with HIVAN were comparable on age, sex, and estimated glomerular filtration rate with those with non-HIVAN kidney disease. There was no statistically significant difference in kidney size comparing those with HIVAN and those without. However, those with HIVAN were less likely to be on cART.

Table 2. Risk factors associated with the presence of HIV-associated nephropathy on biopsy^a

Variable	OR (95% CI)	P value
Age, per yr older	0.95 (0.73–1.24)	0.696
Female vs. male	1.09 (0.67–1.77)	0.722
Mean kidney size, per cm larger	0.98 (0.96–1.01)	0.278
Albumin, per 1 g/dl higher	1.02 (0.77–1.35)	0.882
Hemoglobin, per 1 g/dl higher	1.02 (0.95–1.09)	0.588
cART vs. no cART	0.56 (0.34–0.91)	0.018

cART, combined antiretroviral therapy; CI, confidence interval; OR, odds ratio.

^aAmong 335 patients with non-missing HIV-associated nephropathy and cART status; other missing variables are imputed using multiple imputation.

In adjusted analysis, cART use was significantly associated with a lower risk of HIVAN at the time biopsy (adjusted odds ratio, 0.56 [95% CI, 0.34–0.91], *P* = 0.02). Age, sex, kidney size on ultrasound, albumin levels, and hemoglobin levels were not significantly associated with the presence of HIVAN (Table 2). In the 212 patients who were not on dialysis at the time of biopsy, urine protein/creatinine ratio also showed a statistically significant association with HIVAN (adjusted odds ratio, 1.96 per fold change of urine protein/creatinine ratio [95% CI, 1.29–2.98], *P* = 0.001) (Supplementary Table S2).

Association Between cART, HIVAN, and Death

When stratified by the presence of HIVAN on biopsy and the use of cART, there were differences in survival in unadjusted analysis (log rank test *P* = 0.01) (Figure 1). Patients who were not receiving cART had poorer survival than those who were, regardless of HIVAN status. In adjusted analysis, lack of cART, lower hemoglobin, and the receipt of dialysis at the time of the biopsy procedure were significantly associated with mortality, but HIVAN, age, sex, albumin, and CD4 count were not (Table 3).

Trends Over Time

Throughout the study period (2002–2018), the proportion of patients receiving cART increased and the proportion with HIVAN on at the time of the biopsy

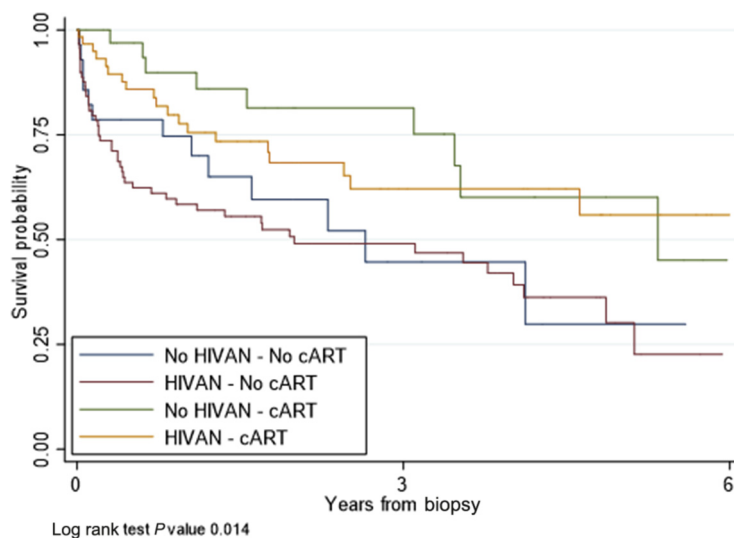


Figure 1. Kaplan–Meier estimates of mortality according to HIV-associated nephropathy (HIVAN) and combined antiretroviral therapy (ART) at biopsy.

procedure decreased. These trends were both statistically significant (P for trend < 0.001) (Figure 2). In 2018, the proportion on cART was 75%.

DISCUSSION

In this cohort study of 419 South African patients diagnosed with HIV referred for a kidney biopsy procedure between 2002–2018, the most common biopsy finding was HIVAN. Those who were diagnosed with HIVAN were comparable with those who were diagnosed with non-HIVAN kidney disease on age, sex, and kidney function. However, those with HIVAN were less likely to be taking cART. When adjusting for covariates, there was a statistically significant difference in risk of death between those with biopsy-proven HIVAN and those with other etiologies, and being on cART at the time of the biopsy procedure was also associated with longer survival. Over the study period, HIVAN incidence decreased and cART use

increased, concomitant with sweeping changes in public health policies in South Africa. These findings show the important role cART plays in mitigating the burden of HIV and HIVAN.

This study expands on previous work that reported the prevalence of biopsy-proven HIVAN in a subset of the study population evaluated from 2005–2008, where the prevalence of HIVAN on biopsy was 57.3%, similar to our study.^{S2} To our knowledge, there are no other biopsy case series published from other African countries in the last decade. However, a comprehensive meta-analysis described the prevalence of chronic kidney disease among people who were HIV-positive in the western, eastern and southern regions of the continent as 9.2%, 5.2%, and 2.3%, respectively.^{S3} In other countries, the prevalence of HIVAN on biopsy has been lower. For example, the prevalence in the United States was 20% in 2010, 29.5% in France in 2011, and 28% in Brazil in 2016.^{S4–S6}

One likely cause for the difference in prevalence of HIVAN in our series compared with those of other countries is the relatively small proportion of patients who were taking cART. Early and timely initiation of cART and suppression of HIV viral load is thought to alter the natural history of HIVAN, preventing its incidence and slowing its progression.^{S4} Before the wide availability of cART, HIVAN progressed inexorably to end-stage kidney disease.^{S7} In South Africa, a key factor that contributed to the low availability of cART was the dissenting political sentiment in the late 1990s and early 2000s.^{3,4} Former President Mbeki did not acknowledge the HIV crisis nor the progression of untreated HIV seropositivity to AIDS and, in so doing, deterred access to cART. Following national and international pressure, a commitment was made in 2003

Table 3. Association of HIV-associated nephropathy and combined antiretroviral therapy at biopsy with mortality adjusted for risk factors^a

Variable	HR (95% CI)	P value
HIVAN vs. no HIVAN	1.63 (0.98–2.72)	0.060
cART vs. no cART	0.59 (0.36–0.97)	0.036
Age, per yr older	1.14 (0.90–1.44)	0.287
Female vs. male	0.81 (0.51–1.27)	0.349
Dialysis at biopsy vs. no dialysis at biopsy	3.02 (1.92–4.73)	0.000
Hemoglobin, per 1 g/dl higher	0.89 (0.80–0.99)	0.029
Albumin, per 1 g/dl higher	0.83 (0.63–1.10)	0.197
CD4 count, per 100 cells/mm ³ higher	0.98 (0.87–1.11)	0.774

cART, combined antiretroviral therapy; CI, confidence interval; HIVAN, HIV-associated nephropathy; HR, hazard ratio.

^aAmong the 233 patients who were not missing HIVAN, cART, and follow-up for mortality; other missing variables are imputed using multiple imputation.

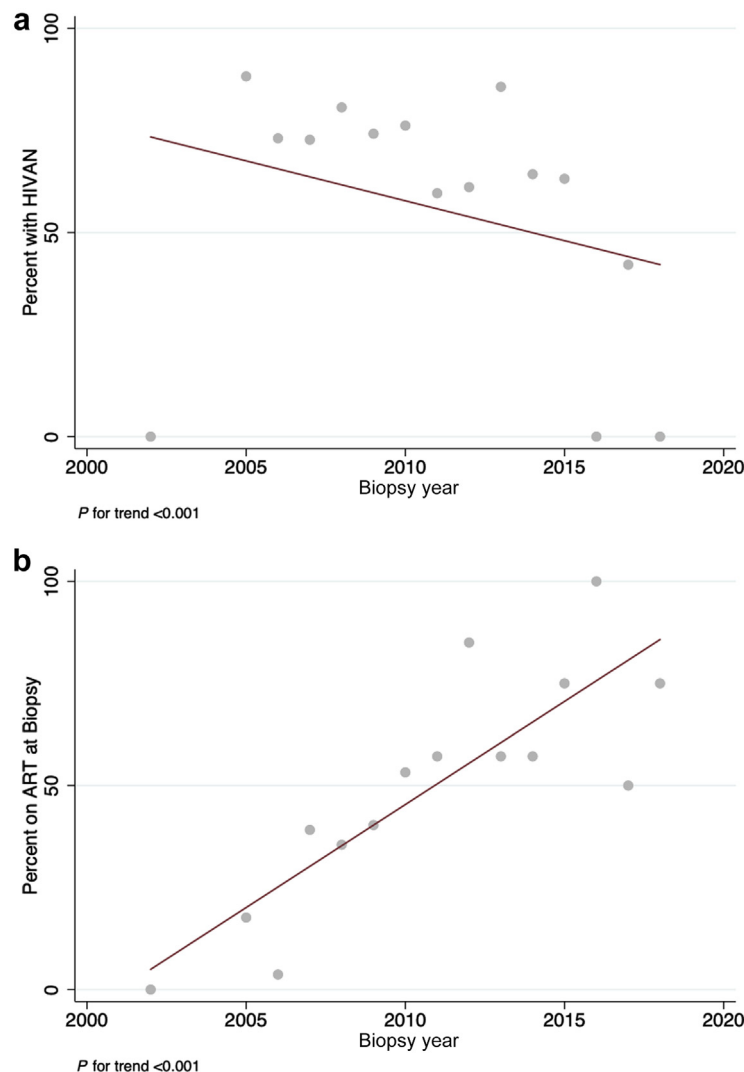


Figure 2. Trends in (a) HIV-associated nephropathy (HIVAN) and (b) combined antiretroviral therapy by calendar year.

to increase the provision of CART in the country.^{S8} South Africa now has the largest ART program in the world, with an estimated 90% of people who are HIV-positive aware of their status and 88% of those on cART are virally suppressed.¹

Our study of black South Africans may represent a particularly high-risk population for the development of HIVAN, notwithstanding access to cART. Some black South Africans possess kidney-risk variants of *APOLI*, which itself is a risk factor for HIVAN.^{6,S7,S9} A 2015 study suggested that black South Africans in Johannesburg who were HIV-positive, cART-naïve, and who had 2 *APOLI* risk variants had 89 times the odds of developing HIVAN compared with HIV-positive control subjects. The estimated prevalence of the *APOLI* high-risk genotype was 79% in those with HIVAN, much greater than the 3.7% in the HIV-positive control subjects.^{S10} Although genetic testing is available in South Africa, it is not done routinely. These estimates may not be representative of the rest of

the country, where genetic variation may exist in subpopulations with different ancestry.^{S11} As such, the true prevalence of *APOLI* risk variants is not known throughout the country.^{S12}

In our study, HIVAN was associated with a higher risk of mortality and cART was associated with a lower risk of mortality. Both observations are consistent with previous literature. Findings in a French study showed a 12% mortality rate among people diagnosed with HIVAN with a median time to death of 24.5 months after HIVAN diagnosis.^{S5} Similar to our findings, a British study reported that cART conferred a greater survival benefit in people with HIVAN.^{S13} In our cohort, the overall mortality rate was higher than these studies, with 34% of the population dying over a median of 2.6 years.

There are some limitations to this study. Our study population was small, derived from routine clinical care, and there were missing data, particularly for viral

load. In addition, the clinical data were from a single tertiary academic center whose patient population might not be reflective of the entire country. Due to the small sample size, we were unable to make meaningful comments on other types of HIV-associated kidney disease, such as tuberculosis-associated glomerular interstitial nephritis, a common etiology in the setting of HIV and one that is associated with early mortality.^{S14}

On the other hand, our study has some notable strengths. South Africa, like most African countries, has a majority black population, an underrepresented population in medical literature. We provide much needed information on an area in which there is limited published literature—HIV-associated kidney disease in Africa—despite being the country with the highest prevalence of HIV in the world.

Our findings highlight the need for obtaining biopsy specimens in people who are HIV-seropositive and have kidney disease, because it is increasingly clear that not all HIV-associated kidney disease among black (South) Africans is HIVAN. We found that HIVAN made up less than two thirds of the HIV-associated kidney disease found on biopsy. Distinguishing between HIVAN and other etiologies is important, because the management of different etiologies may not be the same. There is an important need to increase kidney biopsy registries in both South Africa and the rest of the African continent. As such, it is incumbent to further investigate the changing epidemiology of HIVAN and other HIV-associated kidney pathology to expand our diagnostics to identify other prevalent etiologies and to manage them accordingly.

In summary, in a cohort of 419 HIV-seropositive patients referred for kidney biopsy procedures at a large tertiary academic hospital, HIVAN was the most common biopsy diagnosis. The risk of developing HIVAN was significantly higher among those who were not on cART at the time of the biopsy procedure. In adjusted analysis, both HIVAN and lack of cART were associated with decreased survival. These findings emphasise both the importance of cART initiation in preventing and treating HIVAN and the need for definitive diagnostics to guide treatment and management.

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DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References (PDF)

Table S1. Missing data on baseline characteristics at time of biopsy (PDF).

Table S2. Risk factors associated with the presence of HIVAN on biopsy including urine protein:creatinine.

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