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HIV-associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and pathologic characteristics

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Abstract

Recently, an association was found between non-diabetic kidney disease in African Americans and two independent sequence variants in the *APOL1* gene, encoding apolipoprotein L1. In this study we determined the frequency of *APOL1* risk variants in patients with biopsy-proven HIV-associated nephropathy (HIVAN) and distinctive pathological characteristics potentially driven by those risk variants. Among 76 patients with HIVAN, 60 were successfully genotyped for *APOL1* G1 and G2 polymorphisms. In this cohort, 37 had two risk alleles, 18 were heterozygous and 5 had neither risk variant. There were no differences in the pathological findings of HIVAN and the number of *APOL1* risk alleles. Further, the progression to end stage kidney disease or death did not differ by the number of risk alleles. Median renal survival was 9.3 months in patients with none or one risk allele compared to 11.7 months in patients with two *APOL1* risk alleles. Thus, our study suggests that although the majority of African American patients with HIVAN have two *APOL1* risk alleles, other as yet unknown factors in the host including genetic risk variants and environmental or viral factors may influence the development of this disorder in those with none or one *APOL1* risk allele.

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Introduction

It has long been recognized that individuals with African ancestry with or without HIV infection have higher cumulative lifetime risk of end stage kidney disease (ESKD), higher frequency of kidney disease, and faster progression to ESKD. [1–3] It is calculated that the cumulative lifetime risks for ESKD are 7.8%, 7.3%, 2.5%, and 1.8% for a 20-year-old black woman, black man, white man, and white woman, respectively. [2] Familial clustering of disparate etiologies of kidney disease (e.g., diabetes-attributed ESKD, hypertension-attributed ESKD, and HIVAN) also has been observed in African American families. [4] HIVAN is a distinct phenotype induced by HIV-1 infection and is the most aggressive kidney disease in HIV-1 infected patients. The strong predilection of the disorder for individuals of African descent implies the existence of host genetic variations to explain this racial predilection. A genetic susceptibility locus has been identified in the transgenic mouse model of HIVAN. [5] These animal studies suggested that HIVAN in this setting is linked to susceptibility alleles that along with viral proteins induce latent perturbations in the podocyte gene expression network. [6] In humans, using genome wide mapping by admixture linkage disequilibrium, Kopp *et al.* [7] found several alleles within the *MYH9* gene on chromosome 22 (a gene expressed in glomerular podocytes), with higher frequency among African Americans with HIVAN compared to African American controls. To date, no causal sequence variation in *MYH9* has been identified. It was also noted that many African Americans with HIV-1 infection and who carry these risk alleles at *MYH9* locus do not develop HIVAN, suggesting that other susceptibility factors or “multiple hits” must exist to initiate the disease process. Recently, a stronger association was demonstrated between non-diabetic kidney disease in African Americans and two independent sequence variants in the nearby gene, *APOL1*, encoding apolipoprotein L1. [8, 9] Genovese *et al.* demonstrated an odds ratio of 10.5 (95% CI 6.0 – 18.4) for idiopathic FSGS and 7.3 (95% CI 5.6 – 9.5) for hypertension-attributed ESKD. [8] Similarly, Kopp *et al.* have shown that the presence of two *APOL1* risk alleles is associated with an odds ratio of 17 for primary FSGS and 29 for HIVAN, compared to zero or one *APOL1* risk allele. [10] The *APOL1* risk variants appear to confer resistance to some trypanosomal infections, the cause of African sleeping sickness, which may explain their high frequency in populations of West African descent.[8]

The current study was designed to determine the frequency of *APOL1* risk variants in patients with biopsy-proven HIVAN and examine distinctive pathological characteristics that are potentially driven by those risk variants.

Results

This study included 76 HIV-infected African Americans with biopsy-proven HIVAN. DNA could not be amplified in 17 patients, leaving 61 patients in the study cohort who were successfully genotyped for *APOL1* using kidney biopsy tissue. On pathological review, all HIVAN cases were confirmed as such, except for one case which was determined to have non- collapsing focal segmental glomerulosclerosis (FSGS) and was excluded from the present study. The final analysis was limited to 60 cases, of whom 37 (62%) were homozygous for the G1 and G2 risk alleles, 18 (30%) were heterozygous, and 5 (8%) had neither risk variant.

As shown in Table 1, the proportion of patients with a history of illicit drug use was significantly higher in those with combined 0/1 *APOL1* risk allele compared to those with 2 *APOL1* risk alleles (78.3 vs.47.2% respectively, p=0.03). Even upon the exclusion of those with 0 *APOL1* risk allele, the proportion of patients with a history of illicit drug use was significantly higher in those with 1 *APOL1* risk allele compared to those with 2 *APOL1* risk alleles (77.8 vs.47.2% respectively, p=0.04). There were no significant differences in age, sex, hepatitis C virus co-infection, kidney function, proteinuria, exposure to renin-angiotensin-aldosterone system blockers at the time of biopsy or after biopsy, or steroid therapy at the time of biopsy across the *APOL1* risk allele groups (Table 1). Similarly, there were no differences observed in HIV viral load, CD4+ cell count, or proportion of patients on antiretroviral therapy (ART) at the time of biopsy across the *APOL1* risk allele groups. None of the patients had suppressed viral load defined as <50 copies/ml at the time of the biopsy.

Pathologic characteristics of patients with 2 APOL1 risk alleles

Morphological features of HIVAN by the number of *APOL1* risk alleles are compared in Table 2. The groups were similar, though those with 1/0 *APOL1* risk allele had a trend toward more hyalinosis compared to those with 2 *APOL1* risk alleles, (p=0.05). Severity of disease as manifested by the number of cellular or fibrous crescents, number of collapsed glomeruli, proportion with severe interstitial inflammation, and tubular atrophy was not significantly different across the *APOL1* risk allele groups.

Risk of ESKD and mortality associated with APOL1

During 79.4 person-years of follow-up, progression to ESKD occurred in 31 participants, of whom 22 had 2 *APOL1* risk alleles. Individuals with 2 *APOL1* risk alleles experienced similar progression to ESKD compared to those with 0/1 risk alleles (Figure 1). In the unadjusted analyses, individuals with 2 *APOL*1 risk alleles had similar risk of ESKD compared to those with 0 /1 risk alleles (Table 3). Individuals with diabetes at the time of kidney biopsy had significantly greater risk of ESKD (HR=3.34, CI 1.11–10.05, P<0.03). In the adjusted analyses, increasing age was associated with 6% lower risk of ESKD per year of increase (HR= 0.94, CI 0.88–1, P=0.05). Diabetes remained significantly associated with ESKD risk (HR=18.96 CI 3.38–106.28, P=0.001) (Table 3).

During 238.9 person-years of follow-up, individuals with 2 *APOL1* risk alleles experienced the same mortality compared to those with 1/0 risk alleles (Figure 2). No difference in the combined outcome of ESKD and mortality was observed across the *APOL1* risk allele groups (Figure S1).

Discussion

The study suggests that although the majority of African American patients with HIVAN in our cohort have 2 *APOL1* risk alleles, other unknown genetic risk variants or host factors must exist to explain the development of HIVAN in those with 0/1 *APOL1* risk allele and that the absence of two risk alleles does not exclude the risk for HIVAN in HIV-infected persons. Compared to those with 2 risk alleles, the presence of 1 or no risk alleles was not

correlated with clinical or histologic features in our study. Further, we found that inheritance of 2 copies of *APOL1* risk variants conferred no greater risk of disease progression or mortality than inheritance of 0/1 risk allele.

Genovese *et al*. reported the strongest association signals with FSGS in African Americans in the *APOL1* region rather than in the neighboring *MYH9* region. [8] The *APOL1* missense variants S342G:I384M (G1) and nonsense deletion N388/Y389 (G2) are more strongly associated with ESKD risk than the *MYH9* risk variants. The *APOL1* allele frequency is estimated to be more than 30% in African-Americans while 8–13% of African-Americans carry 2 copies of *APOL1* risk alleles G1 or G2. [8] Our study highlights the high frequency of the 2 *APOL1* risk variants (62%) in patients with HIVAN. This is compared to 21% in patients with type 2 diabetes mellitus (DM) and ESKD, 11% in non-diabetic controls, and 1.8% in type 2 DM without kidney disease. [11] Despite this strong association of *APOL1* risk variants with HIVAN, which may also explain the 3–4-fold increased risk for ESKD in African Americans compared to European Americans in the general population, our study suggests that homozygosity for the G1 or G2 risk alleles is not necessary for the development of HIVAN in HIV-infected individuals. Other chromosome 22 genetic risk variants in addition to *APOL1* risk alleles, the influences of other modifying genes, or non-genetic factors may explain the appearance of HIVAN in those lacking two *APOL1* risk alleles. Therefore, the search for other susceptibility variants in patients with HIVAN remains a critical challenge. Further, it would be premature to recommend genetic testing to identify those at increased risk for HIVAN. Furthermore, it is important to note that the current study only provides an estimate of the sensitivity, not the specificity, of such a screening test.

Histologically, HIVAN is characterized by prominent hypertrophic and proliferating glomerular epithelial cells leading to the formation of pseudocrescents filling Bowman's space, combined with collapse of the glomerular capillary tuft and often with microcystic tubular dilatation. [12] If left untreated, HIVAN almost invariably progresses to ESKD within weeks to months. [13] In this study, *APOL1* risk alleles did not correlate with any histological features of HIVAN or influence progression to ESKD or mortality. This suggests that while *APOL1* variants may confer a risk for HIVAN, they do not influence the pathologic manifestations of the disease and that diverse interaction between genetic background and HIV can produce an identical clinico-pathologic syndrome. Recently, our group in collaboration with others explored the *APOL1* risk variants in HIV-infected individuals with kidney disease other than HIVAN (Fine *et al*., JASN, in press). Notably, 2 *APOL1* risk alleles were found in 63% of individuals with classical FSGS, which is remarkably similar in frequency to those individuals with HIVAN in this study. Thus, this may suggest that *APOL1* strongly increases susceptibly to podocyte injury in African Americans with or without HIV infection. The nature of the resulting histologic injury pattern (glomerulosclerosis or cellular proliferation) may be influenced by other factors that remain to be determined. It could be argued, however, that our patients had quite advanced disease by the time they were diagnosed, and perhaps it was difficult to observe a difference in outcomes at this late stage. Substance use in this cohort involved cocaine, heroin, or both. Cocaine has been demonstrated to be associated with kidney disease in HIV infected

individuals. [14] Interestingly, the proportion with illicit drug use was significantly higher among those with 0 or 1 *APOL1* risk allele and indeed it was significantly higher among those with 1 versus 2 *APOL1* risk alleles. These data would fit with a model of gene-environment interaction, whereby either 2 *APOL1* risk alleles plus HIV infection or 1 *APOL1* risk allele plus HIV infection plus illicit drug use work in synergy to produce HIVAN. Alternatively, it is possible that our study may have been underpowered to detect small differences among the groups.

The mechanism by which *APOL1* risk variants increase susceptibility to non-diabetic kidney disease such as FSGS or HIVAN is undetermined. Glomerular podocytes manifest high levels of autophagy under basal conditions to maintain cellular homeostasis.[15] *APOL1* overexpression induces autophagic cell death in two cancer cell lines[16, 17]; whether these findings are relevant for glomerular cells remains to be determined. On the other hand, inhibition of autophagy using inhibitors of class III phosphatidylinostol 3-kinase such as Wortmannin and 3-methyladenine blocks *APOL1*-induced autophagic cell death. [17] In mice, podocyte-specific deletion of autophagy-related gene 5 (Atg5) leads to a glomerulopathy in aging mice, accompanied by an accumulation of oxidized and ubiquitinated proteins, endoplasmic reticulum stress, and proteinuria. These changes ultimately result in podocyte loss and late-onset glomerulosclerosis. [15] Whether the glomerulopathy that occurs in HIV-1 infected individuals is driven by alteration in autophagic signaling pathways as a result of those specific *APOL1* risk alleles is unclear and requires further investigation.

Our study has a number of limitations. Although our analyses were based on a recessive model for *APOL1* where 2 risk alleles increase risk of disease, others have suggested some increase in risk with a single risk allele. [18] Our study, however, lacked power to distinguish between 0 and 1 risk allele to examine this issue. The biopsies were performed in the context of clinical care, and therefore the timing of the biopsies was not standardized. Nevertheless, the biopsies in both genotype groups were similar in terms of HIV disease (CD4+ cells counts) and kidney disease (mean serum creatinine). Many biopsies were done late in the course of HIVAN, as evidenced by the mean serum creatinine of approximately 5 mg/dL, and this may have limited our ability to discern a difference in progression rate between genotype groups. The number of cases studied was modest, although similar in size to other published studies of HIVAN biopsies. The limited numbers of patients on ACE inhibitor/ARB use at the time of biopsy (n=18) did not allow us to study the potential renal benefit of these agents in this cohort.

In conclusion, our study offers further insights into the genotype/phenotype correlation in African American patients with HIVAN. *APOL1* risk variants strongly increases susceptibly to podocyte injury in African Americans with HIV infection APOL1 or without similar to African Americans without HIV infection noted in other studies. Further work is required to delineate potential interactions between host genetic background, environmental factors, and viral factors that trigger disease initiation as well as progression. Since not all patients with HIV disease and 2 *APOL1* risk alleles develop HIVAN, and others develop HIVAN with 0 or 1 *APOL1* risk allele, it is clear that HIVAN results from a complex interplay of host and viral factors

Materials and Methods

Study Design and Population

Archived percutaneous native kidney biopsies from African-American HIV-infected adults performed at the Johns Hopkins Hospital between January 1996 to December 2009 were collected. Only those with a biopsy report diagnosing HIVAN/collapsing glomerulopathy were included in the study. Biopsies from 78 such patients were obtained for genotyping (see genotyping details below). DNA could not be amplified in 17 patients, leaving 61 patients in the study cohort. This study was approved by the Institutional Review Boards of the Johns Hopkins University School of Medicine and the National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Histopathologic review of biopsy material

Histopathology, of the 61 genotyped cases, original slides were only available on 54 cases (the remaining 7 cases, HIVAN diagnosis was based on pathology reports using the same criteria to define HIVAN) were available and were reviewed by a pathologist masked to the genotype (M.K). After the review, findings were compared with the pathology reports (all performed by pathologists other than M.K.). If the review findings were different from the original report, a second pathologist (L.R), also masked to the genotype, reviewed the slides and made the final ruling on the findings.

Genotyping assay for formalin-fixed paraffin-embedded (FFPE) tissue

Oxidized tissue was removed by cutting five 5 um sections from the face of each FFPE block and five 10 micron sections were cut and placed into 1.5 ml microcentrifuge tubes. 175 uL of microwave retrieval solution (0.1% guanidium thiocyanate and 0.1M NaOH), was added and heated to 100 °C over 10 minutes followed by an additional 10 minutes at 100 °C using the microwave module of a Milestone RH-1 microwave tissue processor (Hacker instruments and industries, Winnsboro, SC).[19] Samples were placed into a Thermomixer (Eppendorf, North America) for 5 minutes at 65° C, and then centrifuged for 5 minutes at 14,000g at 4°C. The lysates were transferred to fresh tubes leaving the paraffin behind. DNA was isolated using the phenol-based AutoGenprep 245T DNA extraction kit according to the method of the manufacturer (Holiston, MA). DNA was suspended in 10 mM Tris, pH 8.0. Yield and purity were determined by NanDrop 1000 spectrophotometer (NanoDrop Technologies, Thermo Scientific, Wilmington, DE). DNA was stored at −20°C until subsequent assay/analyses.

Genotyping APOL1

The *APOL1* G1 allele (comprising SNPS rs73885319 and rs60910145) and the G2 6 base pair deletion (rs717185313) were genotyped by TaqMan assays (ABI, Foster City, CA). Since the HIVAN group is comprised of cases only, we tested the three SNPs for conformance to Hardy-Weinberg expectations using the same TaqMan probes and conditions among an independent set of 383 African Americans subjects using a chi-square goodness of fit test; the SNPs conformed to Hardy-Weinberg expectations ($p>0.05$) in an African American control group (data not shown).

Statistical analyses

Baseline characteristics and renal histopathological findings were compared according to the number of *APOL1* risk alleles using Kruskal-Wallis test for continuous variables and X^2 test for categorical variables. Variables with skewed distributions were $\log_{10}$-transformed.

We evaluated the association of *APOL1* risk alleles with time to ESKD using survival analysis methods. Renal survival times were determined from the time of kidney biopsy to ESKD (defined as an eGFR below 15 mL/min/1.73 m^2 or initiation of dialysis). Participants were censored at the last available visit, death, or the date of June 30, 2011. Kaplan-Meier estimates were calculated, and incident ESKD rates were compared between those with 2 *APOL1* risk alleles versus those with 0 or 1 risk alleles. Unadjusted and adjusted Cox proportional hazards models were constructed to determine the hazard ratio (HR) for ESKD and the corresponding 95% confidence interval. Covariates in the final model were selected based on their clinical and statistical significance on univariate analyses. A parallel survival analysis was conducted to study the association of *APOL1* risk alleles with time to all-cause mortality. Survival times were determined from the time of kidney biopsy to death, and participants were censored at the last available visit or June 30, 2011. Statistical analyses were performed using Stata/MP 11.2 statistical software (StataCorp, College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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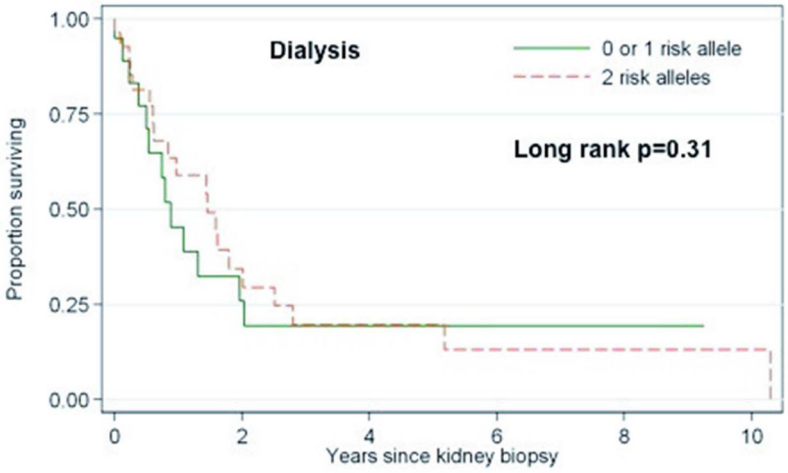

Figure 1.

Kaplan–Meier estimate of renal survival in two groups of study patients (0/1 *APOL1* risk allele and 2 *APOL1* alleles). Median renal survival was 9.3 months (IQR 3.6, 14.6) in patients with 0/1 *APOL1* risk allele compared to 11.7 months (IQR 3.4, 24.5) in those with2 *APOL1* risk alleles, p=0.31 (log rank test).

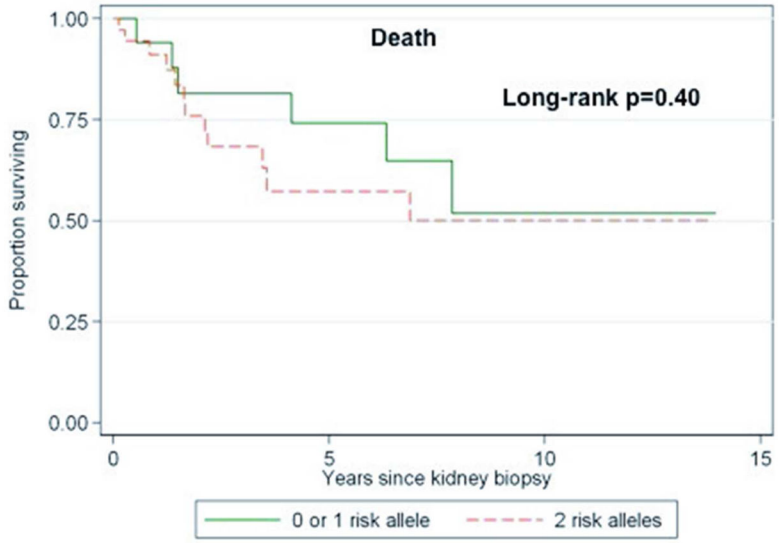

Figure 2.

Kaplan–Meier estimate of survival in two groups of study patients (0/1 *APOL1* risk allele and 2 *APOL1* alleles). Median survival was 34.2 months (IQR 16.6, 77.1) in patients with 0/1 *APOL1* risk allele compared to 20.1 months (IQR 12.5, 34.3) in those with2 *APOL1* risk alleles, p=0.40 (log rank test).

Table 1

Baseline characteristics of the study population

Characteristics	All Patients (N=60)	2 *APOL1* risk alleles (N=37)	1/0 *APOL1*risk allele (N=23)	P-value
Mean age, years (SD)	42.7 (8.1)	41.7 (8.3)	44.3 (7.6)	0.23
Women, n (%)	29 (48)	21 (56.8)	8 (34.8)	0.09
Diabetes, n (%)	6 (10)	2 (5.4)	4 (17.4)	0.13
Hypertension, n (%)	34 (56.7)	22 (59.5)	12 (52.2)	0.58
Hepatitis C, n (%)	32 (53.3)	17 (46.0)	15(65.2)	0.15
Hepatitis B, n (%)	4 (6.7)	2 (5.4)	2(8.7)	0.62
Illicit drug use history, n (%)	35 (59.3) [n=59]	17 (47.2) [n=36]	18 (78.3) [n=23]	0.03
ART use at biopsy, n (%)	13 (24.5) [n=53]	8 (24.2) [n=33]	5 (25.0) [n=20]	1.0
ACE inhibitor/ARB use at biopsy, n (%)	3 (15.8) [n=19]	0.0 (0.0) [n=11]	3 (37.5) [n=8]	0.06
ACE inhibitor/ARB use after biopsy, n (%)	18 (37.5) [n=48]	11 (36.7) [n=30]	7 (38.9) [n=18]	1.0
Glucocorticoid use after biopsy, n (%)	24(46.2) [n=21]	18 (54.6) [n=12]	6 (31.6) [n=9]	0.15
Mean HIV viral load, 1000 copies/ml (SD) at the time of biopsy	194 (218) [n=50]	206 (225) [n=32]	173 (211) [n=18]	0.63
Mean CD4+ cell count, cells/mm^3 (SD)	164 (185)	176 (205)	145 (153)	0.56
Mean Proteinuria, g/24 hours (SD)	8.7 (8.8)	8.4 (8.5)	9.2 (9.5)	0.72
Mean Serum creatinine, mg/dL (SD)	5.4 (3.3)	5.3 (2.7)	5.5 (4.2)	0.79
Mean estimated GFR, ml/min/1.73m^2 (SD)	20.9 (19.3)	18.3 (14.8)	25.2 (24.8)	0.46

Table 2
CORRELATION BETWEEN BIOPSY FINDINGS AND *APOL1* GENOTYPE

Data are presented as mean (SD) or count (percentage). Only subjects with glomeruli≥5 (n=51) were included in analyses denoted (+).

Characteristics	All Patients (N=54)	2 *APOL1* risk alleles (N=32)	1/0 *APOL1* risk allele (N=22)	P-value
Total glomeruli assessed, mean number (SD)	18.2 (10.6)	19.1 (10.9)	16.8 (10.2)	0.40
Cellular crescents+, n (%)				
0	48 (94.1)	30(96.7)	18 (90.0)	
1	2 (3.9)	0 (0.0)	(0.0)	
2	1(2.0)	1 (3.2)	0 (10.0)	0.15
Fibrous crescents+, n (%)				
0	47 (92.2)	28 (90.3)	19 (95.0)	
1	3 (5.9)	3 (9.7)	0 (0.0)	
2	1 (1.9)	0 (0.0)	1 (5.0)	0.15
No. of globally sclerosed gloms+ (SD)	6.8 (8.4)	8.4 (9.9)	4.4 (4.8)	0.21
No. of segmentally sclerosed gloms+ (SD)	1.8 (1.4)	1.7 (2.3)	2 (2.6)	0.36
No. of gloms w/ collapse+ (SD)	2.8 (1.2)	2.9 (1.2)	2.6 (1.2)	0.56
Hyalinosis (%)	27 (50)	12 (37.5)	15 (68.2)	0.05
Severe interstitial inflammation n (%)	15 (27.8)	11 (34.4)	4 (18.8)	0.13
Severe interstitial fibrosis, n (%)	35 (64.8)	22 (68.8)	13 (59.1)	0.50
Severe tubular atrophy, n (%)	34 (63.0)	22 (68.6)	12 (54.6)	0.40
Tubular cysts, n				
0	15 (28.3)	8 (25.0)	7 (33.3)	
1	37 (69.8)	23 (71.9)	14 (66.7)	
2	1 (1.9)	1 (3.1)	0 (0.0)	0.85
Vascular disease, n (%)	24 (44.4)	18 (56.3)	6 (27.3)	0.15

Table 3
Hazard ratios of ESKD associated with *APOL1* risk alleles

Shown are the results for univariable and multivariable models predicting end-stage kidney disease (ESKD). In the multivariable model, only the presence of diabetes was associated with an increased risk for ESKD. eGFR, estimated glomerular filtration rate.

Variable	Univariate		Multivariate	
	Hazard Ratio (95% confidence interval)	P-value	Hazard Ratio (95% confidence interval)	P-value
APOL1, 2 v. 0/1 risk alleles	0.89 (0.43–1.86)	0.76	0.62 (0.27–1.46)	0.28
Age, per year increase	0.99 (0.94–1.04)	0.71	0.94 (0.88–1.0)	0.05
Female	0.59 (0.33–1.85)	0.59	-------- --------	
Hepatitis C antibody seropositivity	1.71 (0.80–3.67)	0.17	-------- --------	
Diabetic	3.34 (1.11–10.05)	0.03	18.96 (3.38–106.28)	0.001
Hypertensive	0.61 (0.30–1.32)	0.21	-------- --------	
HIV-1 RNA level, per $\log_{10}$ 1 copy/ mL higher	1.00 (0.88–1.15)	0.97	-------- --------	
CD4+ cell count, per 1 cell/mm^3 higher	1.00 (0.99–1.00)	0.28	-------- --------	
Baseline eGFR, per 1 mL/min/1.73 m^2 higher	0.99 (0.96–1.01)	0.21	0.98 (0.96–1.01)	0.18
Proteinuric at biopsy mg/g increase	0.97 (0.91–1.03)	0.36	0.96 (0.89–1.03)	0.21