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Apolipoprotein-1 risk variants and associated kidney phenotypes in an adult HIV cohort in Nigeria.

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Authors ' Contributions

CWW and UJW contributed to study development, design, and analysis and were the leads in finalizing the article. MHA assisted the first and senior authors and was the lead in drafting the article. CAW and JBK worked very closely with CWW and MHA on study development and design. BES and HP led the biostatistical components of this study. All authors contributed to the finalization of the study design. All authors also contributed to and approved the final manuscript.

Ethical Considerations

The study was approved by the Institutional Review Board of Vanderbilt University Medical Center (FWA00005756) and the Ethics Committee of AKTH (FWA00026225). The study was registered with clinicaltrials.gov (NCT03201939) and the Pan African Clinical Trials Registry (PACTR201711002808414).

Disclosures

The authors declare that they have no competing interests.

Data sharing

Deidentified patient- and study-level data as well as the study protocol, underlying the results reported in this article will be shared by the corresponding author upon request.

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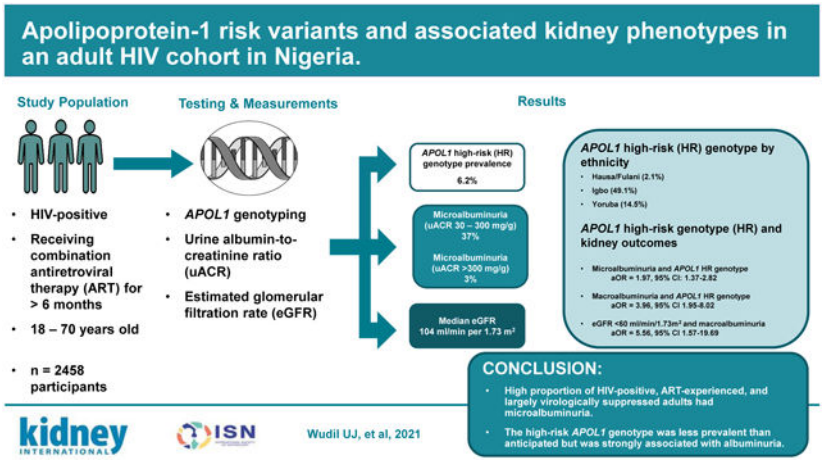
Abstract

HIV-positive adults are at risk for various kidney diseases, and apolipoprotein 1 (APOL1) high-risk genotypes increase this risk. This study aimed to determine the prevalence and ethnic distribution of APOL1 risk genotypes among a cohort of HIV-positive Nigerian adults and explore the relationship between APOL1 risk variant status with albuminuria and estimated glomerular filtration rate (eGFR). We conducted a cross-sectional study among 2 458 persons living with HIV who attended an HIV clinic in northern Nigeria and had received antiretroviral therapy for a minimum of six months. We collected two urine samples four-eight weeks apart to measure albumin excretion, and blood samples to measure eGFR and determine APOL1 genotype. The frequency of APOL1 high-risk genotype was 6.2%, which varied by ethnic group: Hausa/Fulani (2.1%), Igbo (49.1%), and Yoruba (14.5%). The prevalence of microalbuminuria (urine/albumin creatinine ratio 30 – 300 mg/g) was 37%, and prevalence of macroalbuminuria (urine/albumin creatinine ratio over 300 mg/g) was 3%. The odds of microalbuminuria and macroalbuminuria were higher for participants with the APOL1 high-risk genotype compared to those carrying the low-risk genotype ((adjusted odds ratio 1.97, 95% confidence interval 1.37-2.82) and (3.96, 1.95-8.02) respectively)). APOL1 high-risk genotype participants were at higher risk of having both an eGFR under 60 ml/min/1.73m^2 and urine/albumin creatinine ratio over 300 mg/g (5.56, 1.57-19.69). Thus, we found a high proportion of HIV-positive, antiretroviral therapy-experienced, and largely virologically suppressed adults had microalbuminuria. Hence, although the high-risk APOL1 genotype was less prevalent than expected, it was strongly associated with some level of albuminuria.

Graphical Abstract



Keywords

Apolipoprotein 1; microalbuminuria; glomerular filtration rate; HIV; Nigeria; kidney disease

Introduction

Widespread introduction of combination antiretroviral therapy (ART) has markedly reduced HIV-associated morbidity and premature mortality.[1-3] However, as persons living with HIV are surviving longer, incidence of certain non-communicable diseases (NCDs), including HIV-associated kidney disease, is rising among this population.[1-3] HIV-associated kidney disease continues to be a challenge globally, especially in populations of African descent, some of which have genetic susceptibility to kidney disease.[4,5] Chronic kidney disease (CKD), which is often defined as the presence of macroalbuminuria (urine albumin/creatinine ratio [uACR] >300 mg/g) and/or reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73m^2), is at least three- to fourfold more common in sub-Saharan Africa than in resource-replete settings.[6-8] The prevalence of CKD in HIV-positive, ART-naive adults in sub-Saharan Africa ranges from 6 to 48%, with the highest prevalence reported in Nigeria, the most populous nation on the continent.[7-12] Despite evidence of CKD prevalence and impact, there is a paucity of research on the etiology, progression, and prevention of CKD in sub-Saharan Africa. This is especially true for ART-treated persons, who are at increased risk for kidney and potentially other long-term end-organ complications such as cardiovascular and metabolic disease.[11,13-15]

HIV-positive adults are at risk for various kidney diseases, including glomerular and tubulointerstitial diseases associated with infections (e.g. parasitic infections, hepatitis B and C, and with specific medications (e.g. tenofovir disoproxil fumarate [TDF]).[16-24] Certain HIV-related kidney diseases such as HIV-associated nephropathy (HIVAN) and focal segmental glomerulosclerosis (FSGS) also occur almost exclusively (HIVAN) or predominantly (FSGS) in people of African descent.[3] Prior studies have identified genetic markers of susceptibility to CKD in these patients.[16,25-30] Genovese et al. and Tzur et al described two risk alleles (G1 and G2) in the *APOL1* gene encoding apolipoprotein L1.[26,31] The *APOL1* high-risk genotype (defined by the carriage of two *APOL1* risk alleles) confers large odds ratios (ORs) for FSGS (OR = 17), HIVAN (OR = 29 in African Americans and OR = 89 in South Africa), and hypertension-attributed ESKD (OR = 7).[29,32] The highest combined frequency of the G1 and G2 risk alleles has been reported in Nigeria among persons of Yoruba and Igbo descent (~50%).[29,33,34]

Globally, Nigeria has the fourth largest HIV epidemic and among the highest reported frequencies of persons carrying *APOL1* HR alleles.[35] This resource-constrained environment, in which routine screening for kidney disease is uncommon, is an ideal setting to examine the relationship between genetic risk, HIV, and kidney disease. As such, this study aimed to determine prevalence and ethnic distribution of *APOL1* risk among a cohort of HIV-positive, ART-treated Nigerian adults and to explore the relationship between *APOL1* genotype status and markers of CKD, including uACR (including micro- and macroalbuminuria) and eGFR.

Methods

Setting

This study was conducted at the Prof. S.S. Wali Virology Centre of Aminu Kano Teaching Hospital (AKTH), located in Kano, northern Nigeria. The center has been supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) since 2004 and provides comprehensive HIV care and treatment services for more than 10,000 individuals ≥15 years of age.

Study Design

We conducted a cross-sectional study among eligible participants who sought care at AKTH between September 2018 and November 2019. Individuals were eligible for study participation if they were: i) HIV-positive, ii) on ART for a minimum of six months, and iii) between 18 and 70 years of age. The full study protocol has been described previously.[36] In brief, consenting individuals completed three study visits, and medical records were abstracted as described below. At the first study visit (time zero), participants provided comprehensive baseline demographic and clinical information. At the second visit (1- 7 days after the first visit), participants provided one first-morning void urine specimen for measurement of urine albumin/creatinine ratio (uACR). At the third study visit (4-8 weeks after the second visit), participants provided a second first-morning void urine specimen to enable calculation of uACR, as well as a blood sample for measurement of serum creatinine and cystatin C and for *APOL1* genotyping. Seated blood pressure was measured at each scheduled visit using analog sphygmomanometers after at least a five-minute rest.

Serum electrolytes and urine creatinine assays were performed with a Hitachi Cobas C 311 (Roche Diagnostics, Mannheim, Germany) automated analyzer system, using the enzymatic method for urine creatinine estimation. The HemoCue Albumin 201 point of care diagnostic kit (Angelholm, Sweden) was used for urine albumin estimation, using the immunoturbidimetry method.[37,38] For *APOL1* genetic analysis, the plasma buffy coat was isolated, and DNA was extracted using Qiagen extraction kits (Hilden, Germany). Genetic testing and genotyping were done using ThermoFisher Scientific TaqMan custom assays (Waltham, MA) targeting the three chromosome 22 *APOL1* variants associated with CKD, including HIV-associated kidney disease.[39] *APOL1* risk alleles were defined by the presence of G1 and G2 haplotypes. We inferred *APOL1* genotype from the number of risk alleles: individuals were classified as carrying two risk genotypes (G1/G1, G1/G2, or G2/G2), one risk genotype (G0/G1 or G0/G2), or no risk alleles (G0/G0). Each variant was tested for deviations from Hardy-Weinberg equilibrium (HWE) among control subjects using the Chi-square goodness-of-fit test.

Outcome Measures

We selected three primary kidney outcomes: elevated average uACR, elevated serum creatinine, and decreased eGFR. Average uACR was calculated based on two urine specimens collected 4-8 weeks apart, and eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI-Cr-CyC) equation that uses both serum creatinine and cystatin C and is less subject to effects of race, age, and sex compared to creatinine-

based equations.[40-42] Serum creatinine and cystatin C measurements were taken from a single specimen obtained at the final study visit. Because of these limitations, we also considered the proportion of participants having both eGFR < 60 ml/min/1.73m^2 and macroalbuminuria (average uACR value >300 mg/g, based on two determinations 4-8 weeks apart).

Additional Data Elements

Data collected from all participants included age, ethnicity, sex, current medication use (including angiotensin II converting enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARB], and other antihypertensives), comorbid conditions (opportunistic infections, syphilis, cancer, hypertension, other cardiovascular diseases), ART regimen, recent CD4 cell count, and plasma HIV-1 RNA viral load values. These data were obtained directly from the participants during baseline evaluation and through medical record abstraction.

Hypertension was assessed for each participant by both self-report and objective measurement at enrollment. Measurements were classified using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines.[43,44] Normoalbuminuria was defined as average uACR < 30 mg/g, microalbuminuria as average uACR=30-300 mg/g, and macroalbuminuria as average uACR > 300 mg/g. Average body mass index (BMI) was calculated based on measurements taken during each study visit.

Statistical Analysis

Descriptive statistics were summarized overall and by *APOL1* risk category (low risk: 0-1 risk alleles; high risk: any 2 risk alleles) as median (interquartile range [IQR]) for continuous variables and frequency (percent) for categorical variables. Semiparametric cumulative probability models were used to assess the relationship between the three outcomes (uACR, eGFR, serum creatinine) and *APOL1* risk category, adjusted for other covariates.[45] All models were adjusted for age, sex, ethnicity (Hausa/Fulani, Igbo, Yoruba, or other), duration on ART, current use of TDF, CD4 cell count (square root transformed), viral load, diabetes mellitus status, hypertension status, congestive heart failure status, other comorbid condition status, current ACE/ARB use, current smoking status, BMI, and blood pressure category (normal, pre-hypertension, stage 1 hypertension, stage 2 hypertension). Continuous covariates were expanded using restricted cubic splines with three knots to avoid linearity assumptions. Missing data were multiply imputed with 20 imputation replications. The primary analysis dichotomized *APOL1* risk as HR or low risk (LR; 0 or 1 risk allele). Secondary analyses treated *APOL1* as a three-level categorical variable (0, 1, or 2 alleles). Cumulative probability models were fit using logit link functions. The estimated mean and median uACR values, as a function of *APOL1* risk category, holding all other covariates constant at their median or mode values, were extracted from the appropriate fitted cumulative probability models. In additional secondary analyses, outcomes were dichotomized as micro-/macroalbuminuria (uACR > 30 mg/g), macro-albuminuria (uACR > 300 mg/g), reduced eGFR (< 60 ml/min/1.73m^2), and macroalbuminuria plus reduced eGFR (uACR >300 mg/g plus eGFR< 60 ml/min/1.73m^2). Logistic regression models were fit to these dichotomous outcomes. And we used propensity scores to avoid overfitting

in these models. Specifically, propensity scores were computed from a logistic regression model with *APOL1* high-risk status as the outcome and all covariates listed above as predictors; *APOL1* risk status and the logit of the propensity score (i.e., linear predictor from the propensity score model) were included as predictor variables in the final logistic regression models. Analyses were repeated using propensity score matching weights with largely similar results (Supplementary Material Table 1) and covariates were balanced after weighting by the propensity score matching weights (Supplemental Material Figure 1). Statistical analyses were performed using R version 3.6.2. Analysis code is posted at https://biostat.app.vumc.org/wiki/Main/ArchivedAnalyses.

Results

Baseline Cohort Characteristics and Prevalence of APOL1 Risk Alleles

A total of 2 635 participants met eligibility criteria and were approached for potential enrollment. Of these, 2 600 participants (99%) provided informed consent and were enrolled. A total of 100 (4% of those enrolled) were lost to follow-up. Data are presented from 2 458 participants (95% of those enrolled) who completed three study visits over 12 months and had complete data (including genotyping results) available (Figure 1).

Demographic characteristics are described in Table 1. The cohort comprised 1 715 (70%) females and 743 (30%) males. The median [IQR] age was 40 [34, 47] years. Median [IQR] systolic and diastolic blood pressures were 110 [99, 123] mmHg and 73 [66, 81] mmHg, respectively. Median duration on ART was 9 [6, 12] years, 59% were on a TDF-containing regimen at enrollment, the median CD4 cell count was 482 [324, 661] cells/mm^3, and the vast majority (95.8%) were virologically suppressed. Median uACR was 21.7 [9.2, 47.8] mg/g, and median eGFR was 104.3 [87.2, 120.0] ml/min per 1.73 m^2. At first evaluation, 68% of participants had normoalbuminuria, 29% had microalbuminuria, and 3% had macroalbuminuria; at second evaluation, 64% had normo-, 33% had micro-, and 3% had macroalbuminuria. Only 4% had an eGFR <60 ml/min/1.73m^2, and 0.7% had both an eGFR <60 ml/min/1.73m^2 plus uACR > 300 mg/g.

Genetic analyses revealed that 6.2% of participants carried two *APOL1* HR alleles (Table 2). The overall individual risk frequencies for G1 and G2 alleles were 12% and 6.8%, respectively (Table 3). Genotypes were not distributed according to HWE ($P < 0.001$), due to population substructure. However, HWE was restored when calculated for each of the three self-identified ethnicities. The highest frequency of the *APOL1* risk alleles was found in the Igbo ethnic group, with 55 (49%) of Igbo participants having two risk alleles and 42 (38%) having one risk allele (G1 and G2 frequencies: 51% and 17%, respectively). In the Yoruba ethnic group, 8 (15%) participants had two risk alleles and 20 (36%) had one risk allele. Among Hausa-Fulani participants, only 2% had two risk alleles, and 22% had one risk allele (G1 and G2 frequencies: 8% and 6%, respectively). *APOL1* risk allele (0 vs. 1 vs. 2 copies) frequency by ethnicity is shown in Figure 2.

Participants with *APOL1* HR status were more likely to be of Igbo ethnicity ($P<0.001$) and had significantly higher BMI ($P=0.002$), higher uACR ($P<0.001$), higher serum creatinine ($P=0.001$), and lower eGFR ($P=0.004$) than those of LR status. They were also more likely

to have persistent macroalbuminuria (uACR >300 mg/g; P<0.001) and to have both eGFR <60ml/min/1.73m^2 and uACR > 300 mg/g (P<0.001). However, there were no significant differences between *APOL1* LR and HR groups with respect to systolic or diastolic blood pressures, hypertension, use of antihypertensive medications (including ACEi/ARB), or presence of congestive heart failure or other comorbid medical conditions (Table 1).

APOL1 Risk and Key Kidney Parameters

In the primary analysis (Table 4), treating uACR as continuous, *APOL1* HR participants had significantly higher uACR values (adjusted odds ratio [aOR] = 2.16; 95% CI 1.56, 2.98) compared to *APOL1* LR individuals. Holding all covariates constant, the estimated mean uACR was 113 mg/g (95% CI: 78, 148; median: 39 mg/g, 95% CI: 30, 49) for *APOL1* HR participants, compared to 65 mg/g (95% CI: 52, 78; median: 22 mg/g, 95% CI: 19, 26) for *APOL1* LR individuals. In our secondary analysis, dichotomizing the outcome, odds of microalbuminuria were approximately twofold higher for *APOL1* HR participants (aOR = 1.97; 95% CI, 1.37, 2.82). The odds of macroalbuminuria were approximately fourfold higher for *APOL1* HR participants (aOR = 3.96; 95% CI, 1.95, 8.02) compared to *APOL1* LR participants. Finally, *APOL1* HR participants had approximately six-fold higher odds of having both an eGFR < 60 ml/min/1.73m^2 plus uACR > 300 mg/g) (aOR = 5.56; 95% CI, 1.57, 19.69) compared to *APOL1* LR participants. However, HR *APOL1* status was not significantly associated with higher serum creatinine or lower eGFR when considered as continuous variables.

In secondary analyses, having two risk alleles remained a strong predictor of a higher uACR (OR=1.96; 95% CI, 1.41, 2.72) compared to zero risk alleles. However, having 1 risk allele did not increase risk of higher uACR values (OR=0.78; 95% CI, 0.67, 0.92) compared to zero risk alleles. Similar to the primary analysis, there was no significant association between serum creatinine and eGFR for either 1 or 2 risk alleles compared to zero risk alleles (Table 5)

Ethnicity and Key Kidney Parameters

As delineated in Table 6, there were no significant associations between ethnicity and several of the key kidney outcomes including uACR, uACR > 30 mg/g, uACR > 300 mg/g, eGFR, and eGFR <60ml/min/1.73m^2. There was, however, a statistically significant association between the Igbo (aOR = 1.94; 95% CI, 1.33, 2.82), Yoruba (aOR = 1.78 ; 95% CI, 1.12, 2.84), and Other (aOR = 1.47; 95% CI, 1.24, 1.76) ethnic groups with increasing serum creatinine concentration.

Discussion

In this cross-sectional study of HIV-positive, ART-treated adults largely virologically suppressed living in northern Nigeria, *APOL1* genotype prevalence was found to be associated with key kidney function parameters, specifically eGFR and albuminuria (both microalbuminuria and macroalbuminuria).

Only 6.2% of enrolled study participants carried *APOL1* HR genotypes, a lower than expected prevalence, given prior studies in West Africa and African Americans showing

25-50% prevalence.[26,29,32-34,46,47] Earlier studies also showed that *APOL1* risk alleles were found at much lower frequencies (≤10%) throughout sub-Saharan Africa.[26,29,32,47] However, the actual prevalence of *APOL1* G1 (15.3%) and G2 (10%) alleles in our population was lower than previously reported in Nigerian populations.[33,34] There are several possible explanations for this discrepancy. This study was conducted in the northern part of Nigeria where the majority ethnicity is Hausa-Fulani, who have been shown to have very low frequencies of the *APOL1* risk alleles.[33] Our finding that 49% and 15% of those of Igbo and Yoruba ethnicity, respectively, carried the *APOL1* HR genotype was consistent with most previous community-based studies conducted in the regions of Nigeria inhabited by Yoruba and Igbo populations, which reported *APOL1* HR genotype prevalence rates ≥25%.[26,29,34,48] Prevalence of HR genotypes in African Americans who trace their roots to the southern coastline of West Africa, which historically had endemic trypanosomiasis, is similar (~13%) to those of Yoruba ethnicity.[26,29,34,48] This may explain the low *APOL1* HR prevalence among the Hausa-Fulani people, as they historically lived in the transitional zone below the Sahara, outside the trypanosomiasis belt.[33,49-51] We also observed that the *APOL1* genotype frequency distribution did not conform to HWE for all study participants and for those in the “other” category, due to population substructure, but the withingroup genotype frequency distribution by self-reported ethnicity (Hausa-Fulani, Igbo, Yoruba) was concordant with HWE. This varying prevalence of *APOL1* HR genotypes among different ethnic populations, even within one geographic region, may have public health implications, particularly if treatment for *APOL1*-associated kidney disease becomes available. The wide variability in prevalence of *APOL1* HR genotypes among Nigerians also highlights the issues with using self-reported Black race as a surrogate for genetic risk in other settings.

Prevalence of persistent microalbuminuria in our population was 37%. This represents a markedly higher prevalence of microalbuminuria compared to previous results from sub-Saharan Africa, with frequency reported as 11-20%.[52-55] This could be due to TDF use among the majority (59%) of study participants and/or the prevalence of undiagnosed diabetes mellitus and hepatitis B and C infection. It is important to emphasize that the CKD-EPI-Cr-CyC equation (without the race coefficient) was used to estimate GFR. Previous studies have established the advantage of this equation as less subject to the effects of age, sex, muscle mass, diet and race. This is especially relevant given that the study population was entirely Black African.[40]

Further, the *APOL1* HR genotype was a statistically significant predictor of both micro- and macroalbuminuria when compared to the *APOL1* LR genotype; however, other environmental or genetic factors associated with the high rate of proteinuria in the setting of treated HIV infection remain to be identified. Despite the high proportion of participants with microalbuminuria, this was not associated with decreased eGFR in most participants. The mean eGFR for study participants was 104 mL/min/1.73m^2, and frequency of eGFR < 60 ml/min/1.73m^2 was only 4%, compared to prior published studies showing a prevalence of 13-23% among HIV-positive adult populations in sub-Saharan Africa.[7,8,11,41,55-57] This may be related to our study participants being ART-experienced and largely virologically suppressed. It is also possible that many participants with high uACR values are in early stages of either glomerular or tubular damage that is not yet reflected in eGFR.

Neither systolic nor diastolic mean blood pressures were elevated among *APOL1* HR individuals. This finding is consistent with other studies that show HIV-associated kidney diseases do not manifest with elevated blood pressure.[53,55] Although our data showed a slightly higher prevalence of Stage 1 and Stage 2 JNC-7 hypertension among *APOL1* HR participants compared to *APOL1* LR participants, it is not clear whether this finding is due to underlying structural kidney disease or primary hypertension. Other studies have shown an association between *APOL1* risk alleles and elevated blood pressure in HIV-negative adults, with multiple theories about the direction of a potential causal relationship or simultaneous occurrence of the two outcomes (kidney disease and hypertension).[7,10,41,58,59] Our observations may provide helpful data to further examine this important subject. However, our observed low-normal systolic and diastolic blood pressure measurements differ from other studies published among HIV-positive adults in the region.[34,46,53,56,60,61]

Given that poorly controlled HIV infection is a strong driver of HIVAN, it is important to note that our cohort of HIV-positive patients has the following treatment characteristics: on ART for a minimum of six months, with a mean duration on ART of nine years; more than 70% of the cohort on ART for at least six years; and the vast majority (> 95%) virologically suppressed. Our results are also consistent with prior studies that demonstrated the beneficial effects of ART on progressive loss of kidney function.[59,62-64]

Strengths of our study include recruitment of subjects from a large clinical cohort of ART-treated, primarily virally suppressed adults, coupled with *APOL1* genotyping data from this indigenous African population. We were unable to draw definitive conclusions about causal associations due to the cross-sectional design of our study. Also, given that the ethnic composition of the study participants was largely Hausa-Fulani, many smaller ethnic groups were under-represented, particularly the numerous ethnic groups included in the 'Other' category and this might have affected the reported *APOL1* frequencies. We did not exclude individuals with chronic inflammatory conditions, diabetes mellitus, hypertension, and/or physiologic albuminuria. Despite basing our microalbuminuria estimates on two specimens taken four to eight weeks apart, accuracy may be affected by changes in weight, hydration status, general climatic conditions, and inability to definitively ascertain if specimens provided were actually first morning voided urine samples. In addition, to definitively diagnose someone as having CKD, one needs to document persistent kidney damage for three months, whereas our study visits occurred over an average of 2-2.5 months. All participants in this study were ART-experienced and this, in addition to concomitant medications they were receiving to prevent or treat opportunistic infections (i.e. cotrimoxazole (Trimethoprim / Sulfamethoxazole) for *Pneumocystis jiroveci* pneumonia prophylaxis, etc.), placed them at increased risk of nephrotoxicity.[65] In addition, longer-term exposure to the antiretroviral medications (e.g. tenofovir disoproxil fumarate and ritonavir-boosted protease inhibitors) has been strongly associated with decreased GFR.[3,65-68] Additional factors such as immune activation/inflammation resulting from endemic co-infections, as well as environmental exposures (i.e. traditional medications, heavy metals, etc.) may also be contributing to chronic kidney disease risk. There were significant associations between current receipt of TDF, serum creatinine, and eGFR. However, given the cross-sectional nature of this study, we were unable to definitively confirm these associations. Regardless of these limitations, our study provides additional valuable

information in the continuing search for optimal management strategies for *APOL1*-related kidney complications in HIV-positive adults.

In summary, a higher than anticipated proportion of HIV-positive, ART-experienced, and largely virologically suppressed adults had microalbuminuria. We found a significant association between the *APOL1* HR genotype and both micro- and macroalbuminuria, as well as with the presence of both macroalbuminuria and reduced eGFR. In addition, a low proportion of our study population, the majority of whom self-identified as Hausa-Fulani, carried the *APOL1* HR genotype. Future investigations are needed to compare these data with an HIV-negative cohort and to determine the etiology of the high rate of microalbuminuria in this population within the context of controlled HIV infection. Such investigations should include evaluating for immune activation/inflammation from co-infection with certain viruses (e.g. hepatitis B and C), parasites, and tuberculosis, as well as environmental exposures (e.g. traditional medications, heavy metals, etc.). The integration of diagnosis and treatment of kidney disease and other NCDs in HIV-positive persons, including those with the *APOL1* HR genotype, and early intervention in persons with early signs of kidney impairment could help to reduce the burden of NCDs and HIV especially in resource-constrained settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Representatives of the funder (NIDDK) had a role in study design, data analysis, data interpretation, writing of the report, as well as provision of final clearance (following review) for the manuscript to be submitted.

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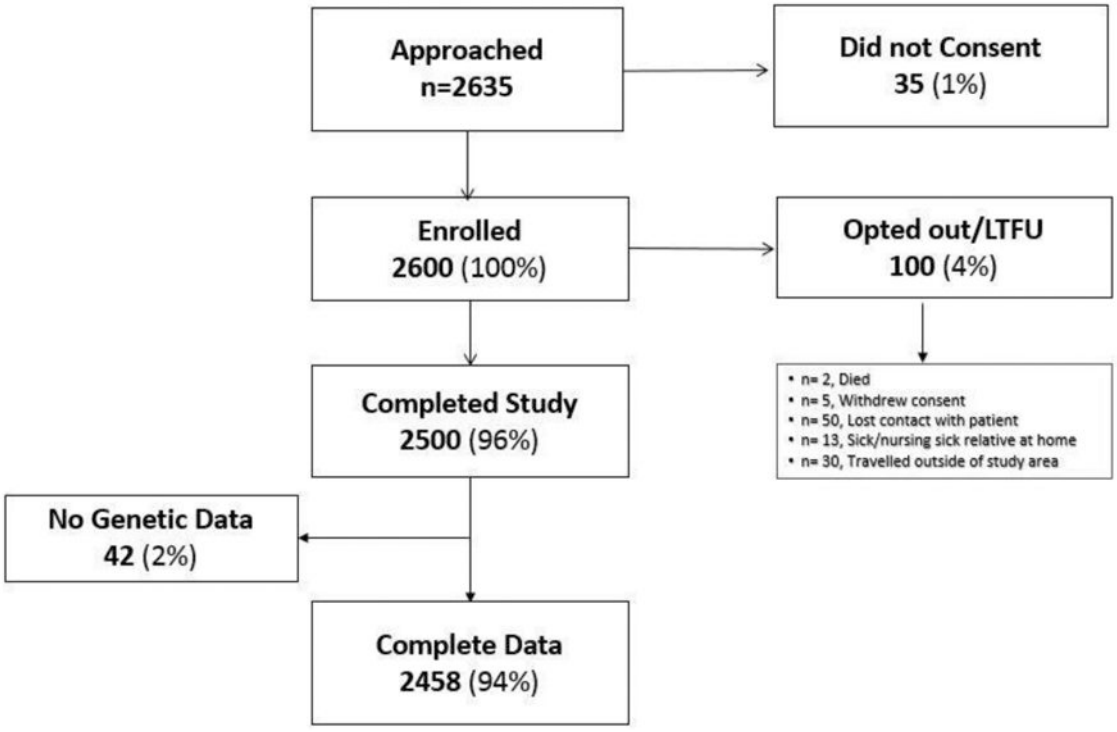

Figure 1:
Study Participant Enrolment Scheme.

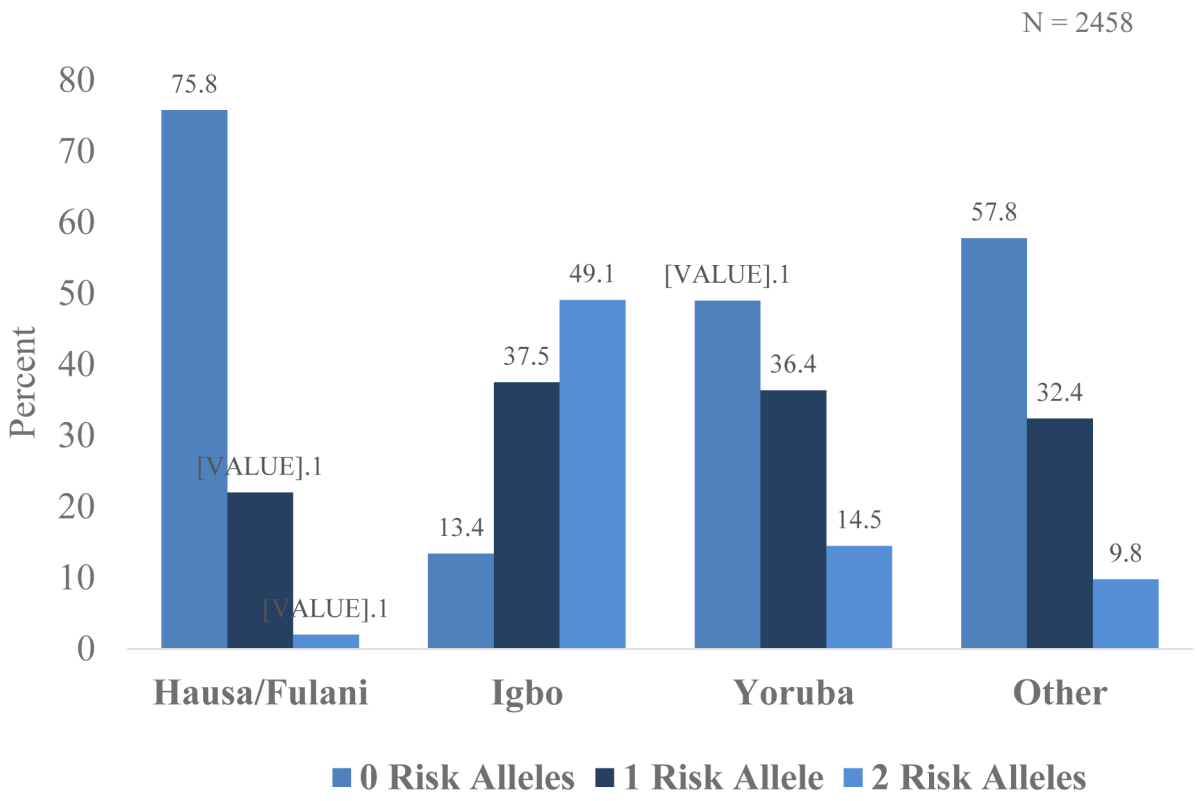

Figure 2: Risk Allele Distribution by Ethnicity
NB: Color is required for this figure in print.

Table 1:

Baseline Characteristics of the Study Population.

Variable	APOL1 Low-Risk (N=2 306)	APOL1 High-Risk (N=152)	Combined (N=2 458)	Test *P*-value
Age; years	40 [34, 47]	40.5 [36, 46]	40 [34, 47]	0.11
Sex; n, %				0.58
Male	694 (30.1)	49 (32.2)	743 (30.2)	
Female	1612 (69.9)	103 (67.8)	1 715 (69.8)	
Ethnicity; n, %				**<0.001**
Hausa/Fulani	1 732 (75.1)	38 (25)	1770 (72.0)	
Igbo	57 (2.5)	55 (36.2)	112 (4.6)	
Yoruba	47 (2.0)	8 (5.3)	55 (2.2)	
Other	470 (20.4)	51 (33.6)	521 (21.2)	
Body mass index (BMI)	23.1 [20.1, 26.8]	24.1 [21.6, 27.5]	23.2 [20.2, 26.9]	**0.002**
Mean Systolic BP (mm Hg)	110 [99, 123]	111 [100, 129]	110 [99, 123]	0.07
Mean Diastolic BP (mm Hg)	73 [66, 80]	74 [67, 83]	73 [66, 81]	0.08
JNC BP Classification; n, %				0.06
Pre-hypertension	511 (22.2)	30 (19.7)	541 (22.0)	
Stage 1 Hypertension	187 (8.1)	21 (13.8)	208 (8.5)	
Stage 2 Hypertension	96 (4.2)	9 (5.9)	105 (4.3)	
Duration on ART (Category); n, %				0.56
< 3 years	148 (6.4)	13 (8.6)	161 (6.6)	
3-6 years	522 (22.6)	32 (21.1)	554 (22.5)	
> 6 years	1 636 (71.0)	107 (70.4)	1 743 (70.9)	
Level of ART Therapy; n, %				0.20
1st Line	1 915 (83.0)	120 (79.0)	2 035 (82.8)	
2nd Line	391 (17.0)	32 (21.1)	423 (17.2)	
Tenofovir (current exposure); n, %	1 347 (58.4)	98 (64.5)	1 445 (58.8)	0.14
Dolutegravir (current exposure); n, %	559 (24.2)	30 (19.7)	589 (24.0)	0.21
Recent CD4 cell count (cells/mm^3)	484 [324, 662]	470 [322.5, 630]	482 [324, 661]	0.61
Recent Viral Load (≤ 200 copies/mL); n, %	2 178 (96.0)	139 (93.3)	2 317 (95.8)	0.12
Diabetes mellitus (self-reported); n, %	47 (2.0)	3 (2.0)	50 (2.0)	0.96
Hypertension (self-reported); n, %	332 (14.4)	29 (19.1)	361 (14.7)	0.11
Congestive Heart Failure (self-reported); n, %	8 (0.4)	1 (0.7)	9 (0.4)	0.54
Other comorbid conditions; n, %	520 (22.6)	25 (16.5)	545 (22.2)	0.08
Taking anti-Hypertensive; n, %	255 (11.1)	24 (15.8)	279 (11.4)	0.08
Taking ACEi/ARB; n, %	116 (5.0)	11 (7.3)	127 (5.2)	0.23
uACR (mg/g);	21.3 [9.1, 46.2]	31.4 [11.9, 75.2]	21.7 [9.3, 47.8]	**<0.001**
Albuminuria Classification; n, %				**<0.001**

Variable	**APOL1 Low-Risk (N=2 306)**	**APOL1 High-Risk (N=152)**	**Combined (N=2 458)**	**Test *P*-value**
Microalbuminuria	846 (36.7)	63 (41.5)	909 (37.0)	
Macroalbuminuria	55 (2.4)	15 (9.9)	70 (2.9)	
Serum Creatinine (mg/dL)	0.78 [0.6, 0.9]	0.83 [0.7, 1.1]	0.78 [0.6, 1.0]	**0.001**
eGFR (ml/min per 1.73 m^2)	104.5 [87.7, 120.2]	101.0 [80.1, 115.1]	104.3 [87.2, 120.0]	**0.004**
eGFR < 60 ml/min per 1.73 m^2 **plus uACR value > 300 mg/g);** n, %	13 (0.56)	5 (3.3)	18 (0.7)	**<0.001**

Statistics presented: Median [IQR]; % (N)

Tests conducted: Continuous variables: Wilcoxon; Categorical variables: Pearson Chi-square.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; uACR, urine albumin-to-creatinine ratio; JNC, joint national committee; ART, combination antiretroviral therapy; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Table 2:

APOL1 risk allele and genotype frequencies.

***APOL1* Risk Allele Genotype**	**Frequency (n = 2 458) (%)**
2 Risk Alleles (High Risk (HR))	**152 (6.2%)**
• **G1/G1**	81 (3.3%)
• **G1/G2**	55 (2.2%)
• **G2/G2**	16 (0.7%)
1 Risk Allele (Low Risk)	621 (25.3%)
0 Risk Alleles	1 685 (68.5%)

Table 3:

APOL1 Risk Allele Distribution

Ethnicity / Risk allele	G1 Allele (N%)					G2 Allele					G1 and G2 haplotypes*				
	−/−	−/G1	G1/G1	MAF** N (%)	HWE *p*-value#	−/−	−/G2	G2/G2	MAF	HWE *p*-value	0 G0/G0	1 G0/G1 G1/G1	2 G1/G1 G1/G2 G2/G2	MAF	HWE *p*-value
	N (%)	N (%)	N (%)			N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	N (%)		
All ***	1 947 (79.2)	430 (17.5)	81 (3.3)	12%	<0.0001	2 141 (87.1)	301 (12.2)	16 (0.7)	6.8%	0.13	1 685 (68.5)	621 (25.3)	152 (6.2)	18.8 %	<0.0001
Hausa /Fulani	1 513 (85.5)	246 (13.9)	11 (0.6)	7.6%	0.77	1 580 (89.3)	182 (10.3)	8 (0.5)	5.6%	0.27	1 342 (75.8)	390 (22.1)	38 (2.1)	13%	0.14
Yoruba	29 (52.7)	21 (38.2)	5 (9.1)	28.2%	0.67	50 (90.9)	5 (9.1)	0 (0)	5%	0.72	27 (49.1)	20 (36.4)	8 (14.5)	33%	0.20
Igbo	31 (27.7)	47 (42)	34 (30.3)	51.3%	0.09	77 (68.8)	33 (29.5)	2 (1.8)	17%	0.47	15 (13.4)	42 (37.5)	55 (49.1)	68%	0.14
Other	374 (71.8)	116 (22.3)	31 (6)	17.1%	<0.0001	434 (83.3)	81 (15.5)	6 (1.2)	8.9%	0.32	301 (57.8)	169 (32.4)	51 (9.8)	26%	0.0003

*Since G1 and G2 are in absolute negative disequilibrium and virtually never occur together on the same chromosome, their allele frequencies can be combined to determine the combined risk allele frequency in a population. G0 represents the haplotype carrying no risk alleles; 0=no variant; 1=carriage of one variant haplotype; 2=carriage of two variant haplotypes.

**Minor allele frequency (MAF)

***Includes all 2458 participants having complete study data

#Hardy Weinberg Equilibrium (HWE) p-value

Table 4:

Association between *APOL1* genotype and kidney parameters.

	Odds Ratio (95% CI) [c]						
	uACR [a]	**uACR > 30mg/g** [b]	**uACR > 300mg/g** [b]	**eGFR** [a]	**eGFR < 60 (ml/min per 1.73 m^2)** [b]	**Serum Creatinine** [a]	**Composite kidney outcome** [b,d]
***APOL1* high risk vs. low risk genotypes**	**2.16 (1.56, 2.98)**	**1.97 (1.37, 2.82)**	**3.96 (1.95, 8.02)**	0.81 (0.59, 1.11)	**2.05 (1.03, 4.07)**	1.17 (0.84, 1.61)	**5.56 (1.57, 19.69)**

[a] From cumulative probability model including the outcome as a continuous variable.

[b] From logistic regression model dichotomizing the outcome and using propensity scores to avoid overfitting models.

[c] All models are adjusted for age, sex, ethnicity, current tenofovir use, CD4 cell count, viral load, diabetes mellitus status, hypertension status, congestive heart failure status, other comorbid condition status, current ACEi/ARB use, current smoking, body mass index, and JNC blood pressure category.

[d] Composite kidney outcome, defined as eGFR < 60 plus uACR > 300 mg/g (macroalbuminuria).

Table 5:

Association between *APOL1* genotype and key kidney parameters.

Risk allele category [a]	Odds Ratio (95% CI) [b]		
	uACR	eGFR	Serum creatinine
1 risk allele	0.78 (0.67, 0.92)	1.02 (0.87, 1.20)	1.04 (0.88, 1.22)
2 risk alleles	1.96 (1.41, 2.72)	1.25 (0.90, 1.72)	1.18 (0.85, 1.65)

[a] *Reference Levels: 0* Risk Alleles (No alleles).

[b] From cumulative probability models including the outcome as a continuous variable. All models are adjusted for age, sex, ethnicity, current tenofovir use, CD4 cell count, viral load, diabetes mellitus status, hypertension status, congestive heart failure status, other comorbid condition status, current ACEi/ARB use, current smoking, body mass index, and JNC blood pressure category

Table 6:

Association between ethnicity and kidney parameters.

Ethnicity	Odds Ratio (95% CI) [c]					
	uACR [a]	uACR > 30mg/g [b]	uACR > 300mg/g [b]	eGFR [a]	eGFR < 60 (ml/min per 1.73 m^2) [b]	Serum Creatinine [a]
Igbo	0.52 (0.36, 0.74)	0.46 (0.29, 0.74)	0.99 (0.34, 2.86)	0.83 (0.57, 1.21)	0.70 (0.24, 2.09)	1.94 (1.33, 2.82)
Yoruba	0.69 (0.44, 1.10)	0.70 (0.39, 1.25)	0.36 (0.04, 2.98)	0.76 (0.48, 1.21)	1.47 (0.47, 4.64)	1.78 (1.12, 2.84)
Other	0.87 (0.73, 1.03)	0.84 (0.68, 1.04)	1.25 (0.68, 2.31)	0.87 (0.73, 1.04)	1.37 (0.84, 2.25)	1.47 (1.24, 1.76)

[a] From cumulative probability model including the outcome as a continuous variable.

[b] From logistic regression model dichotomizing the outcome and using propensity scores to avoid overfitting models.

[c] All models are adjusted for age, sex, ethnicity, current tenofovir use, CD4 cell count, viral load, diabetes mellitus status, hypertension status, congestive heart failure status, other comorbid condition status, current ACEi/ARB use, current smoking, body mass index, and JNC blood pressure category.