Title

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Journal

Clinical Infectious Diseases, 60(4)

ISSN

1058-4838

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Publication Date

2015-02-15

DOI

10.1093/cid/ciu765

Peer reviewed

The Association Between *APOL1* Risk Alleles and Longitudinal Kidney Function Differs by HIV Viral Suppression Status

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Background. Existing data suggest that human immunodeficiency virus (HIV)-infected African Americans carrying 2 copies of the *APOL1* risk alleles have greater risk of kidney disease than noncarriers. We sought to determine whether HIV RNA suppression mitigates *APOL1*-related kidney function decline among African Americans enrolled in the Multicenter AIDS Cohort Study.

Methods. We genotyped HIV-infected men for the G1 and G2 risk alleles and ancestry informative markers. Mixed-effects models were used to estimate the annual rate of estimated glomerular filtration rate (eGFR) decline, comparing men carrying 2 (high-risk) vs 0–1 risk allele (low-risk). Effect modification by HIV suppression status (defined as HIV type 1 RNA level <400 copies/mL for >90% of follow-up time) was evaluated using interaction terms and stratified analyses.

Results. Of the 333 African American men included in this study, 54 (16%) carried the *APOL1* high-risk genotype. Among HIV-infected men with unsuppressed viral loads, those with the high-risk genotype had a 2.42 mL/minute/1.73 m^2 (95% confidence interval [CI], −3.52 to −1.32) faster annual eGFR decline than men with the low-risk genotype. This association was independent of age, comorbid conditions, baseline eGFR, ancestry, and HIV-related factors. In contrast, the rate of decline was similar by *APOL1* genotype among men with sustained viral suppression (−0.16 mL/minute/1.73 m^2/year; 95% CI, −.59 to .27; *P* for interaction <.001).

Conclusions. Unsuppressed HIV-infected African Americans with the *APOL1* high-risk genotype experience an accelerated rate of kidney function decline; HIV suppression with antiretroviral therapy may reduce these deleterious renal effects.

Keywords. HIV; antiretroviral therapy; genetic; kidney disease.

Prior to the advent of highly active antiretroviral therapy (HAART), African Americans infected with human immunodeficiency virus (HIV) were disproportionately at greater risk for end-stage renal disease (ESRD) than non–African Americans [1]. This heightened risk was largely driven by the propensity of HIV-infected African Americans to develop HIV-associated nephropathy (HIVAN), characterized by collapsing glomerulopathy and rapid progression to ESRD. Fortunately, cases of

Received 1 July 2014; accepted 18 September 2014; electronically published 3 October 2014.

[a]Deceased.

Presented in part: American Society of Nephrology Kidney Week, Atlanta, Georgia, 5–10 November 2013.

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Clinical Infectious Diseases® 2015;60(4):646–52

DOI: 10.1093/cid/ciu765

HIVAN are now increasingly rare in developed countries because of effective HIV suppression consequent to earlier and more prevalent HAART use [2]. Nevertheless, HIV-infected African Americans remain at 4-fold greater risk of developing ESRD than European Americans [3].

While differences in social factors, such as access to care, may contribute to persistent racial differences in kidney disease, recent studies strongly support the role of *APOL1* risk alleles in the development of progressive kidney disease among African Americans. In their seminal work, Genovese and colleagues showed that having 2 copies of the *APOL1* G1 and G2 risk alleles, found predominantly among individuals of African descent, was associated with a 5- to 7-fold greater odds of nondiabetic forms of kidney disease (hypertensive nephropathy and focal segmental glomerulosclerosis [FSGS]) among HIV-uninfected African Americans [4]. Subsequent studies demonstrated that these same risk alleles were associated with a >20-fold higher odds of HIVAN [5] as well as a 5-fold greater odds of proteinuria among HIV-infected African Americans [6]. In these studies, risk estimates associated with the G1 and G2 risk alleles among HIV-infected individuals were consistently higher than those observed among HIV-uninfected persons, suggesting a gene–virus interaction. In this study of HIV-infected African Americans in the Multicenter AIDS Cohort Study (MACS), we sought to determine whether HIV RNA suppression modifies the association between *APOL1* risk alleles and longitudinal kidney function.

METHODS

Study Design and Population

We conducted a longitudinal study within the MACS, a prospective cohort study of HIV-infected and -uninfected men who have sex with men followed at 4 sites: Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania [7]. A total of 6972 men were enrolled in 1984–1985, 1987–1990, and 2001–2003. Participants undergo semiannual evaluations consisting of standardized questionnaires, physical examination, and biospecimen collection.

For this substudy, we followed individuals from 31 May 2003 until 31 March 2012. Inclusion criteria were as follows: (1) self-reported African American; (2) HIV-infected; (3) serum creatinine measurements available on at least 3 visits during follow-up; (4) consented to genetic testing; and (5) had data on ancestry informative markers available. The institutional review board of each center approved the study protocols; the Johns Hopkins University Institutional Review Board approved this substudy.

Kidney Function

Serum creatinine has been measured locally at the Los Angeles site using a Beckman-Coulter assay and centrally by the remaining sites using an Olympus assay since 2003. Both assays used a modified Jaffe procedure traceable to isotope dilution mass spectrometry. Longitudinal kidney function was estimated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration glomerular filtration rate (eGFR) estimating equation [8]. Incident CKD was defined by the development of an eGFR <60 mL/minute/1.73 m^2 at 2 consecutive visits among those with an eGFR ≥60 mL/minute/1.73 m^2 at baseline [9].

Genotyping for Ancestry Informative Markers and *APOL1* Risk Alleles

All MACS participants who consented to genetic testing underwent genotyping for 124 single-nucleotide polymorphisms informative of ancestry using the TaqMan OpenArray Genotyping Platform (Applied Biosystems) [10]. To adjust for potential confounding by ancestry, the population substructure was estimated using STRUCTURE, which uses a Bayesian clustering algorithm to group ancestry data [11]. Participants of this substudy were also genotyped for the *APOL1* G1 (nonsynonymous rs60910145 and rs73885319) and G2 (6 base-pair deletion, rs71785313) alleles using TaqMan assays (Applied Biosystems). Individuals carrying 2 copies of the risk alleles (eg, G1G1, G2G2, or G1G2) were categorized as having the high-risk genotype whereas those carrying <2 copies were categorized as having the low-risk genotype.

Additional Variables

Additional data included demographic and clinical characteristics, $CD4^+$ T-cell count (CD4), and plasma HIV-1 RNA level. History of injection drug use was self-reported. Diabetes mellitus was defined by either (1) a fasting serum glucose ≥126 mg/dL or (2) self-reported history of diabetes and use of antidiabetic medications. Hypertension was defined by either (1) a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or (2) self-reported history of hypertension and use of antihypertensive medications. Hepatitis C virus (HCV) coinfection was defined by a positive HCV serum antibody. History of AIDS was based on self-reported AIDS-defining illnesses in the 1993 Centers for Disease Control and Prevention class C definition of AIDS [12]. We defined HAART in accordance with the US Department of Health and Human Services treatment guidelines (http://aidsinfo.nih.gov) as use of at least 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least 1 protease inhibitor (PI) or 1 nonnucleoside reverse transcriptase inhibitor (NNRTI); 1 NRTI in combination with at least 1 PI and at least 1 NNRTI; or an abacavir- or tenofovir-containing regimen that included at least 3 NRTIs in the absence of both a PI and NNRTI, except for the 3 NRTI regimens consisting of abacavir/tenofovir/lamivudine or didanosine/tenofovir/lamivudine [13]. Cumulative years of HAART exposure were calculated from the time of HAART initiation to end of follow-up. Cumulative years of tenofovir exposure were also calculated. HIV-infected men were categorized as

having viral suppression if their HIV-1 RNA load was <400 copies/mL for >90% of their follow-up time.

Statistical Methods

We compared participants' baseline characteristics as well as follow-up time by *APOL1* risk status using *t* test and rank-sum test for continuous variables and χ^2 test for categorical variables. Linear mixed-effect models were constructed to analyze longitudinal eGFRs. Random effects were used to account for the correlation between repeated measurements within individuals. To evaluate differences in the rate of kidney function decline between men having the high- vs low-risk genotype (recessive model), we included an interaction term with follow-up time by *APOL1* risk genotype. Men were censored at the last available follow-up visit or death. For all models, we performed staged adjustments for (1) age, baseline diabetes, and hypertension; (2) baseline HCV antibody serostatus; (3) baseline eGFR; and (4) first 3 clusters of population substructure. We also constructed additional models that adjusted for history of clinical AIDS, time-varying HIV-1 RNA level, and CD4 count as well as cumulative HAART or tenofovir exposure to determine whether these factors influenced our estimates. We then compared whether the rate of annual eGFR decline associated with the *APOL1* high-risk genotype differed between those without vs with sustained viral suppression by inclusion of a 3-way interaction term of time, *APOL1* risk genotype, and viral suppression status in the overall model and by models stratified by HIV RNA suppression status. To determine the robustness of our findings, we conducted sensitivity analyses. First, we alternatively defined HIV RNA suppression as <50 copies/mL for >90% of their follow-up time. Second, we excluded individuals who experienced rapid eGFR change, defined as more than ±10 mL/minute/1.73 m^2 per year (n = 10).

RESULTS

Study Population

Of 375 HIV-infected African Americans with eGFR data available, 23 were excluded for having <3 measurements, and 19 did not have data available regarding genetic ancestry. Therefore, 333 HIV-infected men were analyzed over a median follow-up time of 7.6 years (interquartile range [IQR], 6.7–8.0 years). The median follow-up times were similar by *APOL1* risk status ($P = .49$), as was the number of visits ($P = .54$) (Table 1).

Overall, 54 (16%) participants had the *APOL1* high-risk genotype, whereas 279 (84%) had the low-risk genotype. Table 1 displays the baseline characteristics of participants by *APOL1* risk status. Men with the high-risk genotype were similar to those with the low-risk genotype with regard to age, blood pressure, and comorbid conditions. Mean systolic blood pressures during follow-up were similar between men in the high- and low-risk groups (127 ± 12 vs 125 ± 11 mm Hg, respectively; $P = .27$), as were mean diastolic blood pressures (79 ± 8 vs 78 ± 8 mm Hg, respectively; $P = .46$). However, men with the high-risk genotype had a slightly lower median baseline eGFR of 89.3 mL/minute/1.73 m^2 compared to men with the low-risk genotype (100.1 mL/minute/1.73 m^2; $P < .01$). Those carrying the high- vs low-risk genotype had similar proportions with prior AIDS, HAART receipt, nadir CD4 count <350 cells/μL, and baseline HIV-1 RNA level <400 copies/mL. Tenofovir use

Table 1. Study Participant Characteristics at Baseline by *APOL1* Risk Status

Characteristic	Low-Risk, No. (%) (n = 279)	High-Risk, No. (%) (n = 54)	*P* Value
No. of visits[a]	13.2 (4.2)	13.3 (3.9)	.92
Age, y[a]	42.7 (8.3)	42.3 (8.2)	.76
History of injection drug use	14 (5)	1 (2)	.52
Diabetes mellitus	37 (13)	8 (15)	.93
Hypertension	154 (55)	28 (52)	.76
Hepatitis C virus coinfection	75 (27)	12 (22)	.59
ACE-inhibitor/ARB use	2 (1)	1 (2)	.98
History of AIDS	19 (7)	3 (6)	.97
HAART receipt	205 (73)	41 (76)	.84
Years since HAART initiation[b]	4.6 (2.8–6.7)	3.3 (1.3–6.2)	.04
$CD4^+$ count, cells/μL[b]	509 (331–679)	445 (298–593)	.18
Nadir $CD4^+$ count <350 cells/μL	81 (29)	17 (31)	.89
HIV-1 RNA level <400 copies/mL	138 (53)	28 (55)	.95
Estimated GFR[b], mL/minute/1.73 m^2	100.1 (85.8–117.0)	89.3 (74.1–106.7)	<.01

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; HIV-1, human immuno- deficiency virus type 1.

[a] Mean (standard deviation).

[b] Median (interquartile range).

was reported by 91 (27%) men at baseline and by 252 (76%) during follow-up. The median duration of tenofovir exposure was 3.9 years (IQR, 1.5–6.7 years) and was similar between the 2 *APOL1* risk groups.

Overall Association of the *APOL1* High-Risk Genotype With Longitudinal Kidney Function

During follow-up, 33 individuals developed incident CKD; the proportion of men developing incident CKD was similar across *APOL1* risk and viral suppression groups ($P = .12$). In the overall unadjusted model, HIV-infected men with the high-risk genotype experienced a faster decline in kidney function annually compared to those with the low-risk genotype (β = −.53 mL/minute/1.73 m^2; 95% confidence interval (CI), −.94 to −.12; Table 2). This association remained statistically significant in the fully adjusted model, with HIV-infected men having the high-risk genotype demonstrating a .49 mL/minute/1.73 m^2 (95% CI, −.90 to −.08) greater annual decline in eGFR than men having the low-risk genotype. Further adjustment for AIDS history, cumulative HAART receipt, and time-varying HIV-1 RNA level and CD4 count did not attenuate this association, nor did adjustment for cumulative tenofovir exposure.

Table 2. Overall Association of the *APOL1* High-Risk Genotype With Mean Annual Change in Kidney Function Among HIV-Infected African Americans

Models	Annual Change in eGFR[a]	(95% CI)	*P* Value
1: Unadjusted	−.53	(−.94 to −.12)	.01
2: Adjusted for age, baseline diabetes, and hypertension	−.52	(−.93 to −.11)	.01
3: Additionally adjusted for baseline HCV infection and injection drug use	−.52	(−.93 to −.11)	.01
4: Additionally adjusted for baseline eGFR	−.49	(−.90 to −.08)	.02
5: Additionally adjusted for ancestry[b]	−.49	(−.90 to −.08)	.02
6: Additionally adjusted for AIDS history, cumulative HAART receipt, HIV-1 RNA, and CD4 cell count[c]	−.49	(−.94 to −.04)	.03
7: Model 5 with additional adjustment for AIDS history, cumulative tenofovir receipt, HIV-1 RNA, and CD4 cell count[c]	−.44	(−.87 to −.01)	.04

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1.

[a] In mL/minute/1.73 m^2 per year. Annual change in eGFR values listed in the table correspond to β estimates within the text.

[b] Adjusted for principal components 1–3.

[c] HIV-1 RNA and CD4 cell count were time-varying.

Association of the *APOL1* High-Risk Genotype With Longitudinal Kidney Function Stratified by HIV Suppression Status

To determine whether the accelerated decline in kidney function associated with the *APOL1* high-risk genotype differed between HIV-infected men who had sustained viral suppression during follow-up vs who did not, we conducted analyses stratified by viral suppression status. Among the 83 HIV-infected men who did not achieve HIV-1 RNA levels <400 copies/mL for >90% of their follow-up time, 13 (16%) carried the *APOL1* high-risk genotype. Among the 250 HIV-infected men who maintained viral suppression, 41(16%) had the high-risk genotype. In unadjusted analyses, men who did not achieve sustained HIV RNA suppression experienced faster kidney function decline than did those who had sustained viral suppression (Table 3).

Figure 1*A* demonstrates the steeper decline in the predicted longitudinal eGFRs among men without sustained viral suppression carrying the high-risk vs low-risk genotype whereas Figure 1*B* shows that the predicted longitudinal eGFRs were similar by *APOL1* risk status among those who had sustained viral suppression. Among those with unsuppressed HIV RNA levels, men with the high-risk genotype had a 2.42 mL/minute/1.73 m^2 (95% CI, −3.52 to −1.32) faster annual kidney function decline than men with the low-risk genotype, after adjustment for sociodemographic factors, comorbid conditions, baseline kidney function, baseline CD4 count, AIDS history, and ancestry (Table 3). In contrast, the rate of annual eGFR decline was similar between men with the high- vs low-risk genotype among those with sustained viral suppression (β = −.16 mL/minute/1.73 m^2; 95% CI, −.59 to .27; *P* for interaction <.001).

Similar results were observed in sensitivity analyses. Among men with unsuppressed viral loads (defined as <50 copies/mL for ≤90% of follow-up time), the association between the high-risk genotype and annual rate of eGFR decline remained significant, although somewhat attenuated (β = −1.19 mL/minute/1.73 m^2; 95% CI, −2.03 to −.35). Conversely, among men who maintained viral suppression, the *APOL1* risk genotype was not associated with the annual rate of eGFR decline (β = −.45 mL/minute/1.73 m^2; 95% CI, −.92 to .02; *P* for interaction = .02). After excluding individuals with rapid eGFR change, men with unsuppressed viral loads and the high-risk genotype experienced faster annual eGFR decline (β = −1.24 mL/minute/1.73 m^2; 95% CI, −2.17 to −.31). In contrast, in men with sustained viral suppression, the annual rate of eGFR decline was similar by *APOL1* risk status (β = −.11 mL/minute/1.73 m^2; 95% CI, −.55 to .33; *P* for interaction = .04).

DISCUSSION

Among HIV-infected African Americans, we found that the *APOL1* high-risk genotype was associated with a faster rate of

Table 3. *APOL1* High-Risk Versus Low-Risk Genotype and the Mean Annual Change in Kidney Function by HIV Suppression Status Among HIV-Infected African American Men

	Unsuppressed[a] (n = 83)			Suppressed[a] (n = 250)		
Models	Annual Change in eGFR[b]	(95% CI)	*P* Value	Annual Change in eGFR[b]	(95% CI)	*P* Value
Unadjusted	−2.48	(−3.60 to −1.36)	<.001	−.15	(−.58 to .28)	.51
Adjusted[c]	−2.42	(−3.52 to −1.32)	<.001	−.16	(−.59 to .27)	.46

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

[a] *P* for interaction between *APOL1* genotype, follow-up time, and HIV suppression <.001. Suppressed defined as HIV-1 RNA level <400 copies/mL for >90% of follow-up time.

[b] In mL/minute/1.73 m^2 per year. Annual change in eGFR values listed in the table correspond to β estimates within the text.

[c] Models adjusted for age; baseline diabetes, hypertension, hepatitis C virus infection, and baseline eGFR; ancestry; AIDS history; and baseline CD4 count.

kidney function decline than the low-risk genotype. The more rapid rate of kidney function decline associated with the high-risk genotype was primarily observed among men who did not achieve consistent HIV suppression during follow-up. These individuals experienced a nearly 2.5-fold faster rate of annual kidney function decline than is expected with healthy aging [14]. Conversely, the *APOL1* high-risk genotype was not associated with the rate of kidney function decline among men who maintained durable viral suppression. These results suggest that HIV viremia augments the deleterious renal effects of the *APOL1* risk alleles and that HAART-induced HIV suppression may diminish these deleterious effects. Alternatively, HIV viremia may be a marker of other factors, such as poor adherence to medical care, which may account for our differential observations by HIV suppression status.

The significant associations of the *APOL1* risk alleles with HIVAN and ESRD have been previously demonstrated in HIV-infected African Americans [5, 15, 16]. We showed that HIV-infected individuals with biopsy-proven non-HIVAN kidney disease carrying the high-risk vs low-risk genotype were more likely to have FSGS. Moreover, individuals with the high-risk genotype had a nearly 3-fold increased risk of progressing to ESRD

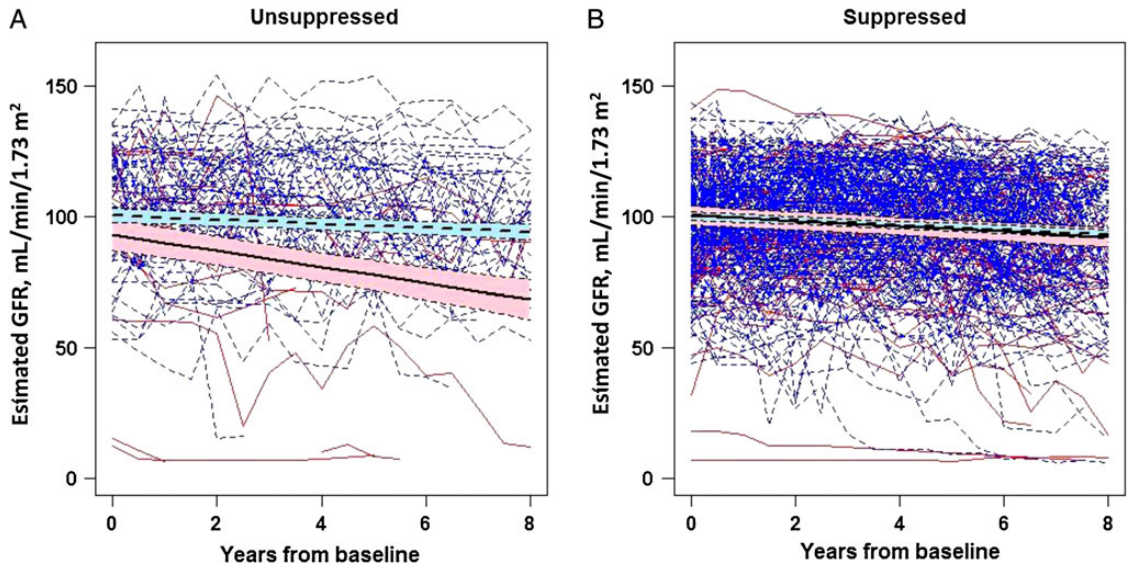

Figure 1. Individual and predicted longitudinal estimated glomerular filtration rate (eGFR) by *APOL1* high-risk status. Solid line signifies the *APOL1* high-risk group while the dashed line signifies the low-risk group. *A*, Longitudinal eGFR for each participant as well as the predicted longitudinal eGFR and corresponding 95% confidence interval (shaded area) among human immunodeficiency virus (HIV)-infected African American men without suppressed viral status (HIV loads <400 copies/mL for >90% of follow-up). *B*, Longitudinal eGFR for each participant as well as the predicted longitudinal eGFR and corresponding 95% confidence interval (shaded area) among HIV-infected African American men with suppressed viral status. All predicted values were centered at age 48 years and baseline eGFR of 98 mL/minute/1.73 m^2 and adjusted for history of diabetes, hypertension, hepatitis C virus serostatus, and ancestry.

[16]. These studies have focused on individuals with advanced CKD who were clinically selected to undergo kidney biopsies. The present analysis builds upon these observations to demonstrate the association of the *APOL1* high-risk genotype with longitudinal kidney function decline and to determine the magnitude of this association in the context of effective antiretroviral therapy.

Our findings are consistent with studies in HIV-uninfected African Americans demonstrating the potential role of the *APOL1* risk alleles in kidney disease progression [17, 18]. In the combined analysis of the African American Study of Kidney Disease and Hypertension and Chronic Renal Insufficiency Cohort, individuals with established CKD and the high-risk genotype experienced a −1.16 to −1.95 mL/minute/1.73 m^2 faster annual rate of kidney function decline than persons with the low-risk genotype [18]. We observed a modest but similar trend among HIV-infected African Americans in the MACS who were predominantly without CKD at baseline. This association, however, was marked among those who did not achieve sustained HIV RNA suppression, and remained strong after adjustment for traditional CKD risk factors such as diabetes and hypertension. In contrast, we observed similar rates of kidney function decline by *APOL1* genotype among HIV-infected men who achieved good virologic control. Our results are consistent with the similar rates of incident CKD by racial/ethnic groups among young HIV-infected persons who were typically initiated on HAART early in the context of accessible healthcare [19].

The differential association of the *APOL1* risk alleles with kidney function decline by HIV RNA suppression status implies a synergistic association with HIV. Our findings are corroborative of a previous case-control study in which Kopp and colleagues reported that the *APOL1* high-risk genotype was associated with a 29-fold greater odds of HIVAN compared to a 16-fold higher odds of HIV-unrelated FSGS [5]. The greater magnitude of association between the *APOL1* high-risk genotype with HIVAN than HIV-unrelated FSGS is consistent with mouse models of HIVAN that demonstrate greater perturbation of the podocyte signaling network in the presence of HIV among genetically susceptible mice [15]. These observations in combination support a gene–virus interaction.

Taylor and colleagues have recently shown that the *APOL1* protein product, apolipoprotein L1, within innate immune cells is upregulated by proinflammatory cytokines such as interferon γ and may inhibit HIV [20]. In contrast, Bruggeman and colleagues showed that plasma apolipoprotein L1 levels did not correlate with proinflammatory cytokines and were similar by *APOL1* genotype among HIV-infected African Americans with CKD (eGFR <60 mL/minute/1.73 m^2 or nephrotic-range proteinuria) and controls [21]. However, cases and controls were matched by HIV-1 RNA level, which diminished the ability to discern correlations between proinflammatory cytokines and apolipoprotein L1 levels across varying levels of viremia. Whether heightened inflammation in HIV infection leads to increased expression of dysfunctional apolipoprotein L1 among carriers of the high-risk genotype needs further study.

A prior study has shown that donor rather than recipient genotype is associated with risk of renal allograft failure, supporting an intrarenal mechanism of injury [22, 23]. Although apolipoprotein L1 messenger RNA is strongly expressed by cryopreserved podocytes, in vitro experiments showed that podocytes also efficiently take up circulating apolipoprotein L1 [24]. Therefore, the relative contribution of intrarenal apolipoprotein L1 production vs circulating levels to kidney disease remains unclear.

Our study is the first to describe the variable association of *APOL1* risk alleles with longitudinal kidney function by extent and degree of HIV RNA suppression. It is also the first study demonstrating a treatment (ie, HAART) that appears to mitigate the enhanced risk of kidney disease associated with *APOL1* risk alleles. This may have important clinical implications, especially in the African continent where the prevalence of the *APOL1* high-risk genotype has been estimated to be as high as 27% in some parts of West Africa [25, 26]. However, our study has a few limitations worth noting. First, the MACS is comprised only of men. Although we do not anticipate sex-based differences in the association of the *APOL1* high-risk genotype with kidney disease, this cohort characteristic may be associated with other unaccounted-for factors that predispose to kidney function decline. Hence, our findings may not be generalizable to the HIV-infected African American population at large. We did not have kidney biopsy data to ascertain the underlying etiology of kidney function decline, although our study allows examination of the association between *APOL1* risk alleles and longitudinal kidney function unbiased by participant selection for kidney disease. As data on proteinuria were not available in the MACS until recently, we were unable to evaluate the association of the *APOL1* high-risk genotype with incident proteinuria or longitudinal changes in proteinuria and its effect modification by HIV RNA suppression status. Finally, we did not have a validation cohort, and replication of our findings will be important to pursue in future studies.

In conclusion, HIV-infected African American men carrying the *APOL1* high-risk genotype experience faster declines in kidney function than men with the low-risk genotype. This *APOL1*-associated accelerated decline occurs primarily among those who do not maintain consistent viral suppression. Conversely, effective antiretroviral therapy appears to reduce the adverse renal effects of the *APOL1* risk alleles. Our findings support a virus–gene interaction; additional studies are needed to find additional treatable factors that lower the risk of *APOL1*-related kidney disease.

Notes

Acknowledgments. We dedicate this manuscript to the memory of our friend and colleague Dr W. H. Linda Kao, and her enduring work on the genetic basis of chronic kidney disease. We are also grateful to the participants of the Multicenter AIDS Cohort Study (MACS).

Disclaimer. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health.

Financial support. M. M. E. received support for this work from the National Institute of Diabetes and Digestive and Kidney Diseases (grant number K23DK081317) and the National Kidney Foundation of Maryland. A. T. is supported by the National Heart, Lung, and Blood Institute (NHLBI) (Cardiovascular Epidemiology Training grant number T32HL007024). Data in this manuscript were collected by the MACS with centers (principal investigators) at Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick) (grant number U01-AI35042); Northwestern University (Steven M. Wolinsky) (grant number U01-AI35039); University of California, Los Angeles (Roger Detels) (grant number U01-AI35040); University of Pittsburgh (Charles Rinaldo) (grant number U01-AI35041); the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson) (grant number UM1-AI35043). The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases, with additional cofunding from the National Cancer Institute. Targeted supplemental funding for specific projects was also provided by the NHLBI and the National Institute on Deafness and Communication Disorders. MACS data collection is also supported by the Johns Hopkins University Institute for Clinical and Translational Research (grant number UL1-TR000424; website located at http://www.statepi.jhsph.edu/macs/macs.html).

Potential conflicts of interest. F. J. P. has received honoraria from Gilead Sciences, Janssen Pharmaceuticals, Merck, and Bristol-Myers Squibb for lectures unrelated to the content of this paper. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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