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Race and Other Risk Factors for Incident Proteinuria in a National Cohort of HIV-infected Veterans

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Abstract

Background—Proteinuria in HIV-infected individuals has been associated with poorer outcomes. We examined risk factors associated with the development of proteinuria in a national registry of HIV-infected veterans.

Methods—21,129 HIV-infected veterans of black and white race without pre-existing kidney disease were receiving health care in the Veterans' Health Administration (VHA) medical system between 1997 and 2011. Using the VHA electronic record system, we identified kidney-related risk factors (hypertension, diabetes, cardiovascular disease), and HIV-related risk factors (CD4 lymphocyte count, HIV RNA level, hepatitis C virus, and hepatitis B virus) for developing proteinuria. Proteinuria was defined by 2 consecutive dipstick measures of 1^+ or higher. The Fine-Gray competing risk model was used to estimate association between clinical variables and incident proteinuria, while accounting for intervening mortality events.

Results—During follow-up (median=5.3 years), 7,031 patients developed proteinuria. Overall, black race compared with white race was associated with a higher risk of proteinuria (HR[95% CI]=1.51[1.43–1.59]), but the association was stronger at younger ages (p interaction<0.001). Age-stratified risk of proteinuria for blacks relative to whites was greatest amongst veterans<30 years (2.19[1.66–2.89]) and the risk diminished with increasing age (1.14[0.97–1.34] for >60 years). We found the race difference to be stronger for the outcome of 2^+ or higher proteinuria (2.13[1.89–2.39]). Both HIV-related and traditional risk factors were also associated with incident proteinuria (p<0.05).

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Conclusions—Compared with whites, risk of proteinuria was higher in black veterans with HIV-infection, particularly at younger ages. In both races, HIV and kidney-related risk factors were associated with higher proteinuria risk.

Keywords

HIV; proteinuria; race

Introduction

Chronic kidney disease (CKD) is defined by either reduced glomerular filtration rate (GFR) or by the presence of proteinuria. CKD has become an important comorbidity among human immunodeficiency virus (HIV)-infected persons.[1] As the survival with HIV infection lengthens, the prevalence of CKD is projected to increase steadily.[2] Proteinuria is often the earliest manifestation of CKD, and is far more prevalent in HIV-infected persons than in similarly aged HIV-negative controls.[3] In addition, among HIV-infected persons, proteinuria is strongly associated with death, cardiovascular disease (CVD) and end-stage-renal-disease (ESRD).[4–7] Previous cross-sectional studies have found that proteinuria is more prevalent among HIV-infected patients who are black[8,9] and have depressed CD4 lymphocyte count.[10] However, few if any studies have evaluated the risk factors of incident proteinuria in HIV-infected patients. To the best of our knowledge, studies have also not examined the risk factors for proteinuria stratified by race; nor have they compared risk factors for mild versus severe proteinuria among HIV-infected patients. In our prior work[11] we have found that the exposure to tenofovir, a first-line treatment of HIV infection, was associated with increased risk of kidney disease events. In this paper our focus is on the associations of race and other risk factors for incident proteinuria in the HIV-infected patients. The purpose of our study was therefore to assess the clinical and demographic factors associated with the development of proteinuria in a prospective cohort of HIV-infected veterans. We hypothesized that both HIV-related and traditional CKD risk factors would contribute to proteinuria risk, and that the magnitude of risk factors would differ between black and white patients.

Methods

We conducted a retrospective cohort study of HIV-infected veterans in the Department of Veterans' Affairs (VA) HIV Clinical Case Registry (CCR) between 1997 and 2011. We studied the association between risk factors and development of incident proteinuria in this national sample of HIV-infected US veterans. Geographically, the Veterans Health Administration (VHA) is national in scope and offers low-cost, comprehensive clinical services to US veterans.[12] The VA HIV CCR actively monitors all HIV-infected persons receiving care in the VA nationally, and automatically extracts demographic, clinical, laboratory, pharmacy, utilization, and death information from the VA electronic medical record to a centralized database.[13]

Patients

We identified 65,675 HIV-infected persons receiving ambulatory care in the VA since 1984. Among these individuals, 30,632 patients initiated ARV therapy in the modern era of combination ARV therapy (after 1997). Inclusion criteria for patients for this study were HIV-infected veterans who were treatment-naïve (i.e. no prior exposure to any ARV) at the time they entered clinical care in the VHA system, and who subsequently received mono or combined ARV after 1997 with regular care and laboratory monitoring. We included patients with defined race of black or white excluding those of other races or missing race. We excluded patients with prevalent kidney failure (receipt of chronic dialysis treatment or kidney transplant), and those who did not have at least one outpatient visit and at least one follow-up proteinuria assessment. We also excluded those with proteinuria present at baseline, leaving 21,129 patients in the analytic cohort. Baseline was defined as the date of starting antiretroviral therapy and they were followed until the first occurrence of proteinuria or death.

Outcomes

The primary outcome was the time from baseline to the time of the first occurrence of proteinuria, defined as two consecutive urinalyses demonstrating a dipstick reading of 1^+ (30 mg/dL) or higher. As a second outcome, we defined “severe proteinuria” as two consecutive dipstick measures of 2^+ (100 mg/dL) or higher. For both outcomes, the event was deemed to have occurred at the time of the second of the two consecutively positive urinalyses.

Predictors and Covariates

Predictor variables were factors hypothesized to be associated with proteinuria in HIV-infected patients. The demographic predictors included age, sex, and race; traditional risk factors included diabetes, hypertension, CVD, dyslipidemia, and eGFR. The HIV-related characteristics included illicit drug use, CD4 lymphocyte count, HIV RNA level, and hepatitis B and hepatitis C co-infection. Additional candidate predictors included body mass index (BMI), low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol, and serum glucose. Age was categorized as <30, 30–40, 41–50, 51–60, and >60 years. BMI was categorized as <20, 20–25, 26–30, and >30 kg/m^2. Absolute CD4 lymphocyte count was categorized as ≤ =200 cells/mm^3 and >200 cells/mm^3. Plasma HIV RNA level was categorized as ≤ =400 copies/mL, 401–10,000 copies/mL, 10,001–100,000 copies/mL, and >100,000 copies/mL. Chronic hepatitis B was defined as a positive surface antigen test (HBsAg), and chronic hepatitis C as a positive antibody test.

Demographic characteristics were obtained from the VA or Medicare health plan databases.[14] Diabetes, hypertension, CVD, smoking, and HIV-related characteristics were ascertained by validated algorithms using a combination of ambulatory diagnoses, physician problem lists, hospitalization discharge diagnoses, procedures, laboratory results, and medication prescriptions.[15–19] Tobacco use was defined by inpatient or outpatient diagnostic codes; questions regarding tobacco use are mandatory in VA clinical care. eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation based on age, gender, race, and serum creatinine level[20]; the MDRD Study equation remains in clinical use in the VA laboratory reporting system. Baseline eGFR was

defined as the average of the first 2 consecutive eGFR measurements after starting ARV therapy separated by at least 3 months. Estimated GFR levels above 120 ml/min/1.73m^2 were capped at this level, as higher estimates are unlikely to be accurate or precise.[21] At any given time, the most recent previous measurement was used to define time-dependent covariates.

Statistical Analyses

Baseline characteristics of the black and white HIV-infected veterans were compared using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Poisson regression models were used to calculate the unadjusted rates of incident proteinuria (per 1000 person-years), stratified for age and race, and rates adjusted for gender, BMI, diabetes, hypertension, dyslipidemia, CVD, smoking, eGFR, illicit drug use, lower CD4 lymphocyte count, higher HIV viral load, and co-infection with hepatitis B and hepatitis C. We investigated the combined effect of risk factors associated with the development of proteinuria in subjects with multiple-record data using the Fine-Gray competing risks analysis.[22] In our cohort, failure could occur due to the onset of proteinuria (failure of interest), or death. To account for the potential bias due to the competing risk of death before onset of proteinuria, we performed the Fine-Gray competing-risks analysis, which extends the Cox proportional hazards model to competing-risks data by simultaneously evaluating hazards for the primary (proteinuria) and competing (death) events. Assumptions of proportional hazards were examined by computing the Schoenfeld residuals.[22,23] We also stratified our analysis by year of diagnosis in order to determine whether the relative contributions of traditional CKD risk factors and HIV-related factors to proteinuria risk changed over time. We conducted a supplemental analysis (competing robustness of the primary results). Tests for interaction were performed using cross-product terms between race and time-dependent characteristics of interest in the model. Because of the observed differences in the association of age and race with proteinuria, analyses were also stratified by black and white race.

We also investigated whether differences in durable viral suppression between blacks and whites partially underlay the differences in proteinuria risk. To evaluate this, we ran our competing risk model initially adjusting for the demographic characteristics and then controlled for all the potential confounders and the viral load. The viral load was controlled in a time-updated fashion so this would account for changes over time in the viral suppression status.

Sensitivity Analysis—Since the frequency of obtaining urine dipsticks may be different in black and white patients, we adjusted our model for the number of times the patient was assessed for proteinuria.

Analyses were conducted using STATA, version 11 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute, Inc. Cary, NC).

Results

Among 21,129 included HIV-infected veterans, median age was 47 years, 97.4% were men, and 52.7 % were black. In general, black patients were less likely to have dyslipidemia and more likely to have hepatitis C virus (HCV), had lower CD4 lymphocyte count, and higher HIV RNA levels (Table 1).

A total of 7,031 proteinuria outcomes were observed during the study follow-up (median duration =5.3 years, IQR 2.3–9.2). The median time between two proteinuria measurements was 5 months (IQR 3–13).

As shown in Figure 1, unadjusted association of age with rate of incident proteinuria per 1,000 patient years differed by race, with a U-shaped association of proteinuria and age in blacks, and a nearly monotonic association in whites. Although blacks appeared to have higher rates of proteinuria within each age category relative to whites, the race difference was greatest among younger patients below age 30 years and gradually diminished with increasing age. Further, the rates were not significantly different at ages > 60 years. This finding persisted after multivariate adjustment, the age specific rates of incident proteinuria per 1000 person-years for both blacks and whites are shown in Table 2. The rate ratio for proteinuria in the <30 year age group was 1.96 (95% CI 1.67–2.30), indicating that blacks were approximately 2 times more likely to have proteinuria than whites in our cohort.

After multivariable adjustment in the competing risk model, low body mass index (BMI) <20 kg/m^2, diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD), and low eGFR prior to the development of proteinuria were all associated with a greater risk of proteinuria (Table 3). HIV-related risk factors were also associated with proteinuria risk: plasma HIV RNA levels > 100,000 copies/mL, CD4 lymphocyte count of ≤200 cells/mm^3, hepatitis C, and hepatitis B virus. We did not observe significant interactions between race and the other covariates (P interaction>0.05 in fully adjusted models) except for the interaction between age and race for the risk of proteinuria (p<0.001) and eGFR and race (p=0.0012) in our multivariable analysis. Although higher eGFR was associated with a lower risk of proteinuria in both blacks and whites, the association was somewhat stronger in whites (HR [95% CI]= 0.91 [0.89–0.94] vs. HR [95% CI]= 0.95 [0.93–0.96]).

In race-stratified analysis, the hazard ratios associated with the risk factors were similar in blacks and whites. Table 4 shows the further exploration of the race differences for risk of proteinuria using age-stratified multivariable analysis. The results showed a 2-fold for blacks vs. whites among participants below 30 years of age. With increasing age, the risk associated with race difference lost its significance. Given the non-linear association with age, we also ran our multivariable competing risk model for time to proteinuria with a linear and a quadratic term for age rather than the age categories as shown in Table 3. For estimating the risk of proteinuria, the adjusted HR for black vs. white was 1.38 (95% CI 1.31–1.45).

Additional analyses stratified by the year of HIV diagnosis, showed a lower incidence among those diagnosed in more recent years. However, risk factor associations with proteinuria were generally consistent across the four time-periods (Supplemental Table 2).

Black race was consistently associated with an elevated risk of proteinuria across years of follow-up relative to whites; the hazard ratio for blacks relative to whites was 1.46 [95% CI: 1.33–1.60] among persons diagnosed prior to 1997; 1.60 [1.45–1.75] for diagnosis between 1997–1999; 1.55 [1.40–1.71] for diagnosis between 2000–2003; and 1.44 [1.28–1.62] for diagnosis after 2003.

On evaluating whether differences in durable viral suppression between blacks and whites partially underlay the differences in proteinuria risk, we found that the race effect was significant regardless of the effect of durable viral suppression both in simple demographic adjusted analysis (1.39 [1.33–1.46]) and in adjusted models excluding viral load (1.50 [1.43–1.58]). Rather the race effect strengthened after adjusting the model for viral load (1.51 [1.43–1.59]).

Sensitivity Analysis

We were concerned that race might influence ascertainment of urine protein, so we adjusted for number of times the patient was assessed for proteinuria. The association of black race with proteinuria risk remained significantly stronger in this adjusted model (HR [95% CI]: 1.50 [1.43–1.59]).

Severe Proteinuria—Of the 21,129 HIV-infected individuals in the cohort who had urine analyses documented, 1,390 developed severe proteinuria (Table 5). Severe proteinuria was defined as two consecutive dipstick measures of 2^+ (100 mg/dL) or higher. After adjustment for confounders, individuals of black race had a 2-fold risk of severe proteinuria compared with white individuals. In this analysis, the interaction of race and age was less striking (p=0.002). The model indicated that as age increased by a decade, the risk of severe proteinuria observed for the race difference decreased by 19%. Among the traditional risk factors for kidney disease, hypertension, diabetes, CVD, and lower eGFR were each associated with higher risk of severe proteinuria. Multivariable-adjusted associations of the HIV disease risk factors such as low CD4 lymphocyte count, high viral load, hepatitis C and hepatitis B co-infections with severe proteinuria were also stronger.

In the stratified analysis, risk factors had similar associations among blacks and whites. HIV RNA level had a somewhat stronger association in blacks than in whites (p for interaction=0.08).

Discussion

Proteinuria is part of the definition of CKD, and is a risk marker for progression to ESRD.[24] Previous literature found that higher levels of proteinuria are independently associated with risk of ESRD at all levels of eGFR.[25] Our study examined the risk factors for proteinuria among a large cohort of HIV-infected veterans. Black race has been found to be a strong risk factor for advanced HIV-associated nephropathy[5,10] but little data are available on the risk of developing proteinuria in HIV-infected individuals. In addition, fewer studies have been conducted in the era of highly effective antiretroviral (ARV) therapy in large number of patients. One such study is our previous work on the association of tenofovir, a first-line treatment of HIV infection that is currently used in half of all the antiretroviral regimens,

with proteinuria.[11] To our knowledge, our study is the largest cohort of HIV-infected veterans used to date to investigate the risk factors for the development of proteinuria.

Our study demonstrates a significant effect of race on the incidence of proteinuria and severe proteinuria. Furthermore, we found that the higher risk of incident proteinuria in blacks was particularly evident in younger age groups. In our cohort, the younger blacks compared to the younger whites were not under control for hypertension and diabetes (Supplemental Table 1). Another potential reason could be that risks in younger blacks are driven by early susceptibility due to genetic polymorphic difference (i.e. interaction of APOL1 genotype) that may contribute to the increasing risk of proteinuria.[26,27] Several studies have demonstrated significant disparities in HAART utilization according to race. HIV-infected blacks present for care in more advanced stages of disease[28] and are less likely to receive HAART than are HIV-infected whites, even among patients in care.[29] The differences in proteinuria risk across races could be further attributed to the differences in durable viral suppression between blacks and whites as demonstrated in our study. Since black race is a strong risk factor for HIV associated renal disease, as has previously been documented,[7,30] and young black men are disproportionately affected,[31] the stronger association of black race with proteinuria in the younger groups is not surprising. Nevertheless, these striking racial differences with age in development of proteinuria among patients with HIV highlight the critical need for studies devoted to the understanding of underlying disease mechanisms for HIV-related kidney disease, particularly among blacks.

Previous studies investigating predictive factors of CKD have identified hypertension and diabetes to be independently related to CKD.[32,33] It is noteworthy that in the competing risk framework, the key established kidney and cardiovascular risk factors of kidney dysfunction were associated with the risk of incident proteinuria, including dyslipidemia and CVD along with diabetes and hypertension. Interestingly, in our study these traditional risk factors exhibited a stronger association with severe proteinuria.

Our study also demonstrated that several HIV-related risk factors including elevated HIV RNA level, absolute CD4 lymphocyte count, hepatitis C, and hepatitis B co-infection are associated with proteinuria and their association is much stronger with severe proteinuria. Our finding of higher HIV RNA levels and lower CD4 lymphocyte counts predictive of proteinuria in multivariable analysis, was consistent with the findings from the Women's Interagency HIV Study.[10] The significance of HIV RNA level and CD4 lymphocyte count in this analysis supports the hypothesis that HIV-related renal diseases[34,35] represent a direct infection of the virus within the kidney and viral suppression caused by highly active antiretroviral therapy (HAART) likely results in improvement or stabilization of renal function.[21] In this cohort, a positive test for the hepatitis C antibody was also an independent predictor of proteinuria.

Our study is unique as it is a large, national registry investigating incident proteinuria with the relatively uniform health care system available to US veterans and the reliable data source for both the predictor variables and the outcome of proteinuria. Due to the large size, we have substantial power in our cohort to compare risk factors among the black and white veterans. Prior studies that have identified risk factors of proteinuria in HIV infection were

cross-sectional and therefore causality cannot be inferred. Our database includes 21,129 HIV-infected veterans who met the inclusion criteria and were followed for a median duration of 5.3 years. This represents the largest study to evaluate incident proteinuria with longitudinal data on urine protein excretion in black and white race.

Despite the strengths mentioned of this study, there are certain limitations. First, this study is predominantly in male veterans receiving care in the Department of VA Health Care System, so results may not be generalizable to women, non-veterans, or racial and ethnic groups other than blacks and whites. Second, assessment of proteinuria was at discretion of clinicians and not part of a protocol. Third, we did not study any specific glomerular or tubular markers of injury due to sustained proteinuria. Fourth, we cannot determine the role of apolipoprotein L1 (APOL1) genotype as a determinant of risk for proteinuria in the HIV-infected blacks. Previous studies, however, have demonstrated an 8–13% prevalence of the APOL1 genotype in HIV-infected blacks.[26,27] Fifth, we excluded patients with missing race information and those who reported being American Indians/Native Alaskan, Pacific Islander/Native Hawaiian or Asian (19%) from our cohort. Sixth, we did not have HCV RNA data to confirm chronic HCV infection, and it is likely that Hepatitis C resolved in some patients.

In summary, we found remarkably strong associations between black race and incident proteinuria that were strongest among younger HIV-infected individuals and for the outcome of severe proteinuria. These differences raise the need to understand the alarmingly high risk of proteinuria in blacks. Further, clinicians should recognize that both the traditional and HIV-related risk factors are important contributors to the onset of proteinuria. The potential impact of these results includes the possibility of improving intervention and prevention/control and delay the onset of proteinuria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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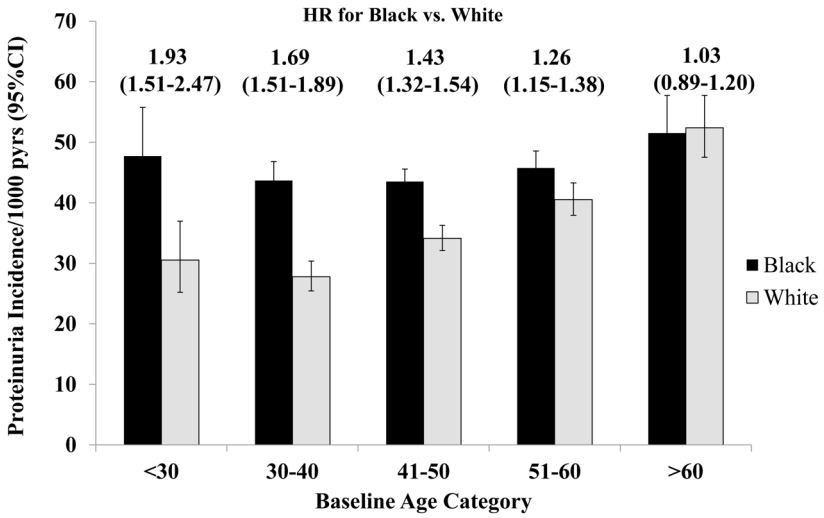

Figure 1.

Unadjusted incidence rates of dipstick proteinuria, stratified by race and age (bars with 95% CI). Numbers on top of the columns represent unadjusted hazard ratios for the race difference within age categories (with 95% CI).

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Table 1

Baseline clinical characteristics of 21,129 HIV-infected persons without baseline proteinuria, stratified by race [*]

	Overall (n=21,129)	Black (n = 11,143)	White (n = 9,986)	P-value
Follow-up time, years (Median, IQR)	5.3, 2.3–9.2	5.0, 2.2–8.9	5.7, 2.4–9.4	<0.0001
Age, years	47 (41, 54)	47 (41, 53)	48 (40, 55)	<0.0001
<30	910 (4.3%)	473 (4.2%)	437 (4.4%)	<0.0001
30–40	3936 (18.6%)	2015 (18%)	1921 (19%)	<0.0001
41–50	8188 (38.8%)	4674 (42%)	3514 (35%)	<0.0001
51–60	5888 (27.9%)	3082 (28%)	2806 (28%)	<0.0001
>60	2207 (10.4%)	899 (8.1%)	1308 (13%)	<0.0001
Female, %	556 (2.6%)	379 (3.4%)	173 (1.7%)	<0.0001
Comorbid Conditions, %				
Hypertension	5741 (27%)	3088 (28%)	2607 (26%)	0.0086
Diabetes	1202 (5.6%)	679 (6.1%)	506 (5.1%)	0.0012
Dyslipidemia	3555 (17%)	1455 (13%)	2067 (21%)	<0.0001
Smoking (Ever Use)	4010 (19%)	2006 (18%)	1974 (20%)	0.0011
Hepatitis C Virus	5069 (24%)	3067 (28%)	1976 (20%)	<0.0001
Measurements				
CD4+ Count, cells/mm^3	320 (164, 514)	296 (143, 479)	348 (190, 558)	<0.0001
HIV Viral Load (1000 copies/mL)	10 (0, 83)	15 (0, 87)	6 (0, 77)	<0.0001
Illicit drug use	5448 (26%)	3094 (28%)	2354 (24%)	<0.0001
Systolic blood pressure, mmHg	127 (116, 139)	127 (115, 139)	127 (116, 138)	0.88
Diastolic blood pressure, mmHg	77 (70, 85)	78 (70, 86)	77 (70, 84)	<0.0001
Body mass index, kg/m^2	25 (22, 28)	25 (22, 28)	25 (22, 28)	0.0015
<20	2025 (9.6%)	1217 (11%)	808 (8.3%)	<0.0001
20–25	8701 (41.2%)	4514 (42%)	4187 (43%)	<0.0001
26–30	6957 (32.9%)	3492 (32%)	3465 (36%)	<0.0001
>30	2864 (13.6%)	1588 (15%)	1276 (13%)	<0.0001
Total cholesterol, mg/dL	172 (145, 203)	169 (142, 198)	177 (149, 208)	<.0001
Triglycerides, mg/dL	140 (95, 219)	126 (87, 189)	160 (107, 249)	<.0001
Low density lipoprotein, mg/dL	101 (78, 127)	99 (76, 125)	103 (81, 130)	<.0001

	Overall (n=21,129)	Black (n = 11,143)	White (n = 9,986)	P-value
High density lipoprotein, mg/dL	38 (31, 49)	41 (32, 51)	36 (29, 45)	<.0001
Glucose, mg/dL	95 (87, 106)	94 (86, 106)	96 (88, 107)	<.0001
Albumin, g/dL	3.9 (3.6, 4.3)	3.9 (3.5, 4.2)	4.0 (3.7, 4.3)	<.0001
eGFR, mL/min/1.73m^2	95 (81, 110)	100 (85, 116)	90 (78, 104)	<.0001
eGFR <60mL/min/1.73m^2, %	901 (4.2%)	422 (3.8%)	477 (4.8%)	0.0004
ACE/ARB use	1327 (6.3%)	735 (6.6%)	592 (5.9%)	0.046

* Continuous variables reported as median (IQR). Proteinuria defined by urinalysis protein 30 mg/dL or greater.

Abbreviations: Estimated glomerular filtration rate (eGFR); Angiotension converting enzyme/Angiotensin II receptor blockers (ACE/ARB); interquartile range (IQR).

Table 2

Adjusted* incidence rates of dipstick proteinuria events per 1,000 person-years, stratified by race and age

	Black			White			Incidence Rate Ratio
Age Group	**N**	**Events**	**Adjusted Event Rate**	**N**	**Events**	**Adjusted Event Rate**	
<30	473	159	73.9 (63.9, 85.4)	437	105	39.0 (32.2, 47.3)	1.96 (1.67, 2.30)
30–40	2,015	794	59.1 (55.1, 63.3)	1,921	491	33.2 (30.5, 36.2)	1.63 (1.50,1.77)
41–50	4,674	1,780	55.3 (52.7, 58.1)	3,514	1,037	38.7 (36.3, 41.2)	1.56 (1.46,1.67)
51–60	3,082	1,086	62.1 (58.4, 66.1)	2,806	879	44.4 (41.4, 47.6)	1.47 (1.34,1.61)
>60	899	297	66.2 (58.6, 74.7)	1,308	403	53.6 (48.2, 59.6)	1.34 (1.16,1.54)

*Adjusted for age, gender, race, BMI, diabetes, hypertension, dyslipidemia, CVD, smoking, eGFR, CD4 count, viral load, and co-infection with hepatitis B and hepatitis C

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Table 3

Hazard ratios and 95% CI for Dipstick Proteinuria (n=7,031 events) in 21,129 HIV-infected Participants* by Fine-Gray Competing Risk Model.

Characteristic	Proteinuria**		
	Overall	Black	White
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Female	0.92 (0.78, 1.07)	0.95 (0.80, 1.14)	0.79 (0.57, 1.09)
Age (in years) < 30	1.37 (1.18, 1.58)	1.72 (1.41, 2.10)	1.09 (0.87, 1.37)
30–40	1.13 (1.02, 1.25)	1.41 (1.22, 1.63)	0.90 (0.78, 1.05)
41–50	1.04 (0.95, 1.14)	1.21 (1.05, 1.38)	0.93 (0.82, 1.06)
51–60	0.98 (0.89, 1.08)	1.07 (0.93, 1.23)	0.95 (0.84, 1.08)
>60	Reference	Reference	Reference
Black vs. White	1.51 (1.43, 1.59)		
BMI (in kg/m^2) < 20	1.19 (1.08, 1.31)	1.10 (0.97, 1.25)	1.32 (1.12, 1.54)
20–25	1.04 (0.97, 1.12)	1.02 (0.92, 1.12)	1.07 (0.95, 1.20)
26–30	0.94 (0.88, 1.02)	0.92 (0.83, 1.01)	0.98 (0.87, 1.10)
>30	Reference	Reference	Reference
Smoking (yes/no)	1.08 (1.01, 1.15)	1.13 (1.05, 1.23)	1.00 (0.91, 1.10)
Diabetes (yes/no)	1.63 (1.52, 1.75)	1.60 (1.46, 1.75)	1.71 (1.54, 1.89)
Hypertension (yes/no)	1.26 (1.19, 1.33)	1.31 (1.22, 1.40)	1.17 (1.08, 1.28)
Dyslipidemia (yes/no)	1.28 (1.21, 1.36)	1.25 (1.16, 1.34)	1.30 (1.19, 1.42)
CVD	1.31 (1.21, 1.40)	1.33 (1.20, 1.47)	1.26 (1.13, 1.40)
eGFR (per 10 ml/min/1.73 m^2)	0.93 (0.92, 0.94)	0.95 (0.93, 0.96)	0.91 (0.89, 0.94)
Illicit drug use	1.08 (1.02, 1.15)	1.06 (0.98, 1.15)	1.13 (1.02, 1.25)
CD4<200 cells/mm^3	1.09 (1.03, 1.16)	1.09 (1.01, 1.18)	1.10 (1.00, 1.21)
Viral Load (copies/mL)			
≤400	Reference	Reference	Reference
401–10,000	0.85 (0.80, 0.92)	0.89 (0.82, 0.98)	0.81 (0.73, 0.91)
10,001–100,000	1.15 (1.05, 1.26)	1.19 (1.06, 1.32)	1.09 (0.94, 1.26)
>100,000	1.12 (1.01, 1.25)	1.11 (0.98, 1.26)	1.16 (0.97, 1.38)
HBV	1.13 (1.06, 1.21)	1.15 (1.05, 1.25)	1.11 (1.00, 1.24)

Characteristic	Proteinuria**		
	Overall	Black	White
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
HCV	1.21 (1.14, 1.27)	1.21 (1.13, 1.30)	1.23 (1.14, 1.34)

Note: The results are shown for the models including the overall and stratified by the two available races.

* participants with proteinuria at baseline are excluded.

** Proteinuria is defined as two consecutive urinalyses demonstrating a dipstick reading of 1^{+} (30 mg/dL) or higher.

Abbreviations: BMI, body mass index (kg/m^2); CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HCV, Hepatitis C virus; HBV, Hepatitis B virus.

Table 4

Hazard ratios and 95% CI for Proteinuria in 21,129 HIV-infected Participants by Fine-Gray Competing Risk Model, stratified by age

	Black vs. White
Age Group	**Adjusted HR (95% CI)**
<30	2.19 (1.66, 2.89)
30–40	1.77 (1.57, 1.99)
41–50	1.53 (1.41, 1.66)
51–60	1.41 (1.29, 1.55)
>60	1.14 (0.97, 1.34)

Adjusted for age, gender, race, BMI, diabetes, hypertension, dyslipidemia, CVD, smoking, eGFR, illicit drug use, CD4 count, viral load, and co-infection with hepatitis B and hepatitis C

Table 5

Hazard ratios and 95% CI for Severe Proteinuria (n=1,390 events) in 21,129 HIV-infected Participants* by Fine-Gray Competing Risk Model.

Characteristic	Severe Proteinuria**		
	Overall	Black	White
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Female	0.56 (0.35, 0.87)	0.61 (0.38, 0.98)	0.29 (0.07, 1.18)
Age (in years) < 30	1.33 (0.88, 2.01)	1.27 (0.74, 2.20)	1.59 (0.84, 3.00)
30–40	1.31 (1.05, 1.65)	1.52 (1.13, 2.04)	1.07 (0.73, 1.58)
41–50	1.29 (1.06, 1.57)	1.38 (1.06, 1.80)	1.22 (0.89, 1.68)
51–60	1.07 (0.87, 1.31)	1.03 (0.78, 1.36)	1.22 (0.90, 1.66)
>60	Reference	Reference	Reference
Black vs. White	2.13 (1.89, 2.39)		
BMI (in kg/m^2) < 20	1.07 (0.86, 1.32)	0.78 (0.60, 1.02)	1.92 (1.31, 2.82)
20–25	0.98 (0.83, 1.16)	0.85 (0.70, 1.03)	1.31 (0.97, 1.77)
26–30	0.95 (0.80, 1.12)	0.89 (0.73, 1.09)	1.07 (0.78, 1.47)
>30	Reference	Reference	Reference
Smoking (yes/no)	1.06 (0.93, 1.22)	1.10 (0.94, 1.29)	0.98 (0.75, 1.26)
Diabetes (yes/no)	2.10 (1.85, 2.39)	2.05 (1.75, 2.40)	2.29 (1.82, 2.87)
Hypertension (yes/no)	1.79 (1.59, 2.01)	1.86 (1.61, 2.14)	1.62 (1.33, 1.99)
Dyslipidemia (yes/no)	1.28 (1.12, 1.45)	1.20 (1.03, 1.40)	1.41 (1.12, 1.78)
CVD	1.51 (1.31, 1.75)	1.51 (1.26, 1.81)	1.44 (1.12, 1.84)
eGFR (per 10 ml/min/1.73 m^2)	0.81 (0.79, 0.83)	0.82 (0.80, 0.85)	0.78 (0.74, 0.82)
Illicit drug use	0.99 (0.86, 1.13)	1.02 (0.87, 1.20)	0.94 (0.73, 1.21)
CD4<200 cells/mm^3	1.18 (1.04, 1.34)	1.22 (1.05, 1.42)	1.11 (0.88, 1.39)
Viral Load (copies/mL)			
≤400	Reference	Reference	Reference
401–10,000	0.96 (0.82, 1.13)	1.00 (0.82, 1.22)	0.92 (0.70, 1.21)
10,001–100,000	1.42 (1.18, 1.70)	1.55 (1.25, 1.92)	1.15 (0.81, 1.63)
>100,000	1.41 (1.17, 1.71)	1.43 (1.16, 1.78)	1.37 (0.93, 2.02)
HBV	1.14 (0.99, 1.32)	1.17 (0.99, 1.39)	1.09 (0.83, 1.41)

Characteristic	Severe Proteinuria**		
	Overall	Black	White
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
HCV	1.34 (1.20, 1.51)	1.36 (1.19, 1.57)	1.39 (1.13, 1.70)

Note: The results are shown for the models including the overall and stratified by the two available races.

* participants with proteinuria at baseline are excluded.

** Severe proteinuria is defined as two consecutive dipstick measures of 2^+ (100 mg/dL) or higher

Abbreviations: BMI, body mass index (kg/m^2); CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HCV, Hepatitis C virus; HBV, Hepatitis B virus.

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